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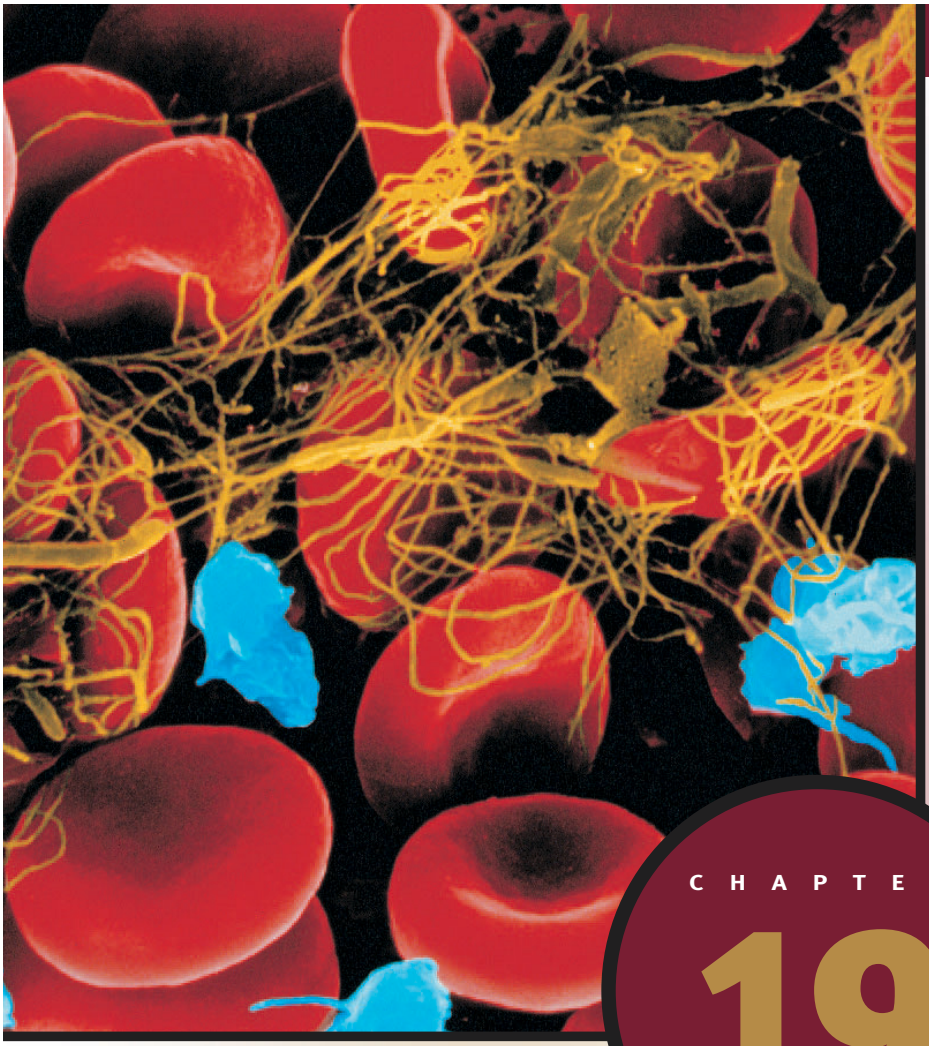


Colorized scanning electron micrograph (SEM) of a blood clot. The red discs are red blood cells, the blue particles are platelets, and the yellow strands are fibrin.

Cardiovascular System

Blood

CHAPTER 19

Many cultures around the world, both ancient and modern, share beliefs in the magical qualities of blood. Blood was considered the "essence of life" because the uncontrolled loss of it can result in death. Blood was also thought to define our character and emotions. People of a noble bloodline were described as "blue bloods," whereas criminals were considered to have "bad" blood. It was said that anger caused the blood to "boil," and fear resulted in blood "curdling." The scientific study of blood reveals characteristics as fascinating as any of these fantasies. Blood performs many functions essential to life and often can reveal much about our health.

Blood is a type of connective tissue, consisting of cells and cell fragments surrounded by a liquid matrix. The cells and cell fragments are the formed elements, and the liquid is the plasma. The formed elements make up about 45%, and plasma makes up about 55% of the total blood volume (figure 19.1). The total blood volume in the average adult is about 4–5 L in females and 5–6 L in males. Blood makes up about 8% of the total weight of the body.

Cells require constant nutrition and waste removal because they are metabolically active. The cardiovascular system, which consists of the heart, blood vessels, and blood, connects the various tissues of the body. The heart pumps blood through blood vessels, and the blood delivers nutrients and picks up waste products.

This chapter explains the *functions of blood* (640), *plasma* (641), and the *formed elements* (642) of blood. *Hemostasis* (650), *blood grouping* (655), and *diagnostic blood tests* (658) are also described.

Functions of Blood

Objective

- ***Explain the functions of the blood.***

Blood is pumped by the heart through blood vessels, which extend throughout the body. Blood helps to maintain homeostasis in several ways.

1. *Transport of gases, nutrients, and waste products.* Oxygen enters blood in the lungs and is carried to cells. Carbon dioxide, produced by cells, is carried in the blood to the lungs, from which it is expelled. Ingested nutrients, ions, and water are transported by the blood from the digestive tract to cells, and waste products of cells are transported by the blood to the kidneys for elimination.
2. *Transport of processed molecules.* Many substances are produced in one part of the body and transported in the blood to another part where they are modified. For example, the precursor to vitamin D is produced in the skin (see chapter 5) and transported by the blood to the liver and then to the kidneys for processing into active vitamin D. Active vitamin D is transported in the blood to the small intestines, where it promotes the uptake of calcium. Another example is lactic acid produced by skeletal muscles during anaerobic respiration (see chapter 9). Lactic acid is carried by the blood to the liver, where it is converted into glucose.

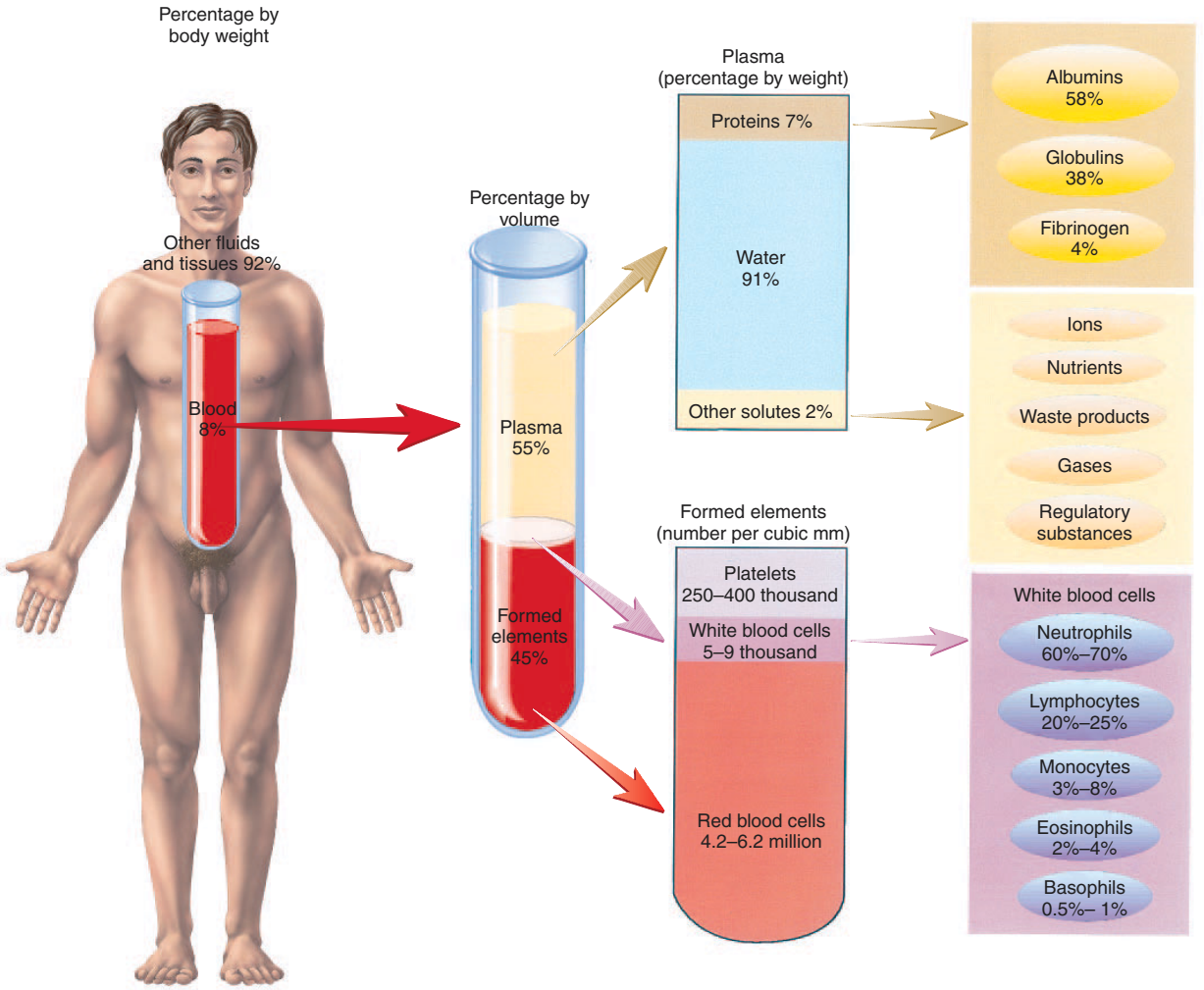


Figure 19.1 Composition of Blood

Approximate values for the components of blood in a normal adult.

3. *Transport of regulatory molecules.* Many of the hormones and enzymes that regulate body processes are carried from one part of the body to another by the blood.
4. *Regulation of pH and osmosis.* Buffers (see chapter 2), which help keep the blood's pH within its normal limits of 7.35–7.45, are in the blood. The osmotic composition of blood is also critical for maintaining normal fluid and ion balance.
5. *Maintenance of body temperature.* Blood is involved with body temperature regulation because warm blood is transported from the interior to the surface of the body, where heat is released from the blood.
6. *Protection against foreign substances.* Cells and chemicals of the blood make up an important part of the immune system, protecting against foreign substances such as microorganisms and toxins.
7. *Clot formation.* Blood clotting provides protection against excessive blood loss when blood vessels are damaged. When tissues are damaged, the blood clot that forms is also the first step in tissue repair and the restoration of normal function (see chapter 4).

1. List the ways that blood helps to maintain homeostasis in the body.

Plasma

Objective

- *List the components of blood plasma, and explain their functions.*

Plasma (plaz′mă) is the liquid part of blood. It's a pale yellow fluid that consists of about 91% water and 9% other substances, such as proteins, ions, nutrients, gases, and waste products (table 19.1). Plasma is a **colloid** (kol′oyd), which is a liquid containing suspended substances that don't settle out of solution. Most of the suspended substances are plasma proteins, which include albumin, globulins, and fibrinogen. **Albumin**

Table 19.1 Composition of Plasma

Plasma Components	Function
Water	Acts as a solvent and suspending medium for blood components
Plasma Proteins	
Albumin	Partly responsible for blood viscosity and osmotic pressure; acts as a buffer; transports fatty acids, free bilirubin, and thyroid hormones
Globulins	Transports lipids, carbohydrates, hormones, and ions like iron and copper; antibodies and complement are involved in immunity
Fibrinogen	Functions in blood clotting
Ions	
Sodium, potassium, calcium, magnesium, chloride, iron, phosphate, hydrogen, hydroxide, bicarbonate	Involved in osmosis, membrane potentials, and acid–base balance
Nutrients	
Glucose, amino acids, triacylglycerol, cholesterol	Source of energy and basic "building blocks" of more complex molecules
Vitamins	Promote enzyme activity
Waste Products	
Urea, uric acid, creatinine, ammonia salts	Breakdown products of protein metabolism; excreted by the kidneys
Bilirubin	Breakdown product of red blood cells; excreted as part of the bile from the liver into the intestine
Lactic acid	End product of anaerobic respiration; converted to glucose by the liver
Gases	
Oxygen	Necessary for aerobic respiration; terminal electron acceptor in electron-transport chain
Carbon dioxide	Waste product of aerobic respiration; as bicarbonate, helps buffer blood
Nitrogen	Inert
Regulatory Substances	Enzymes catalyze chemical reactions; hormones stimulate or inhibit many body functions

(al-bū′min) makes up 58% of the plasma proteins and is important in the regulation of water movement between tissues and blood. Because albumin doesn't easily pass from the blood into tissues, it plays an important role in maintaining the osmotic concentration of blood (see chapters 3 and 26). **Globulins** (glob′ū-linz) account for 38% of the plasma proteins. Some globulins, such as antibodies and complement, are part of the immune system (see chapter 22), whereas others function as transport molecules (see chapter 17). **Fibrinogen** (fī-brin′ō-jen) constitutes 4% of the plasma proteins and is responsible for the formation of blood clots (see "Coagulation" on p. 651).

The water, proteins, and other substances in the blood, such as ions, nutrients, waste products, gases, and regulatory substances, are maintained within narrow limits. Normally, water intake through the digestive tract closely matches water loss through the kidneys, lungs, digestive tract, and skin. Therefore, plasma volume remains relatively constant. Suspended or dissolved substances in the blood come from the liver, kidneys, intestines, endocrine glands, and immune tissues like the spleen. Oxygen enters blood in the lungs and leaves the blood as it flows through tissues. Carbon dioxide enters blood from the tissues and leaves the blood as it flows through the lungs.

2. *Define the term plasma. What are the functions of albumin, globulins, and fibrinogen in plasma? What other substances are found in plasma?*

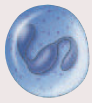
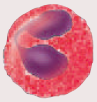
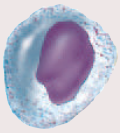
Formed Elements

Objectives

- *Describe the origin and formation of the formed elements.*
- *Describe the structure, function, production, and breakdown of red blood cells.*
- *Describe the structures and functions of white blood cells and platelets.*

About 95% of the volume of the **formed elements** consists of red blood cells, or erythrocytes (ĕ-rith′rō-sītz). The remaining 5% consists of white blood cells, or leukocytes (loo′kō-sītz), and cell fragments called platelets, or thrombocytes (throm′bō-sītz).

Table 19.2 Formed Elements of the Blood

Cell Type	Illustration	Description	Function
Red blood cell		Biconcave disk; no nucleus; contains hemoglobin, which colors the cell red; 7.5 µm in diameter	Transports oxygen and carbon dioxide
White blood cell		Spherical cell with a nucleus; white in color because it lacks hemoglobin	Five types of white blood cells, each with specific functions
Granulocytes			
Neutrophil		Nucleus with two to four lobes connected by thin filaments; cytoplasmic granules stain a light pink or reddish purple; 10–12 µm in diameter	Phagocytizes microorganisms and other substances
Basophil		Nucleus with two indistinct lobes; cytoplasmic granules stain blue-purple; 10–12 µm in diameter	Releases histamine, which promotes inflammation, and heparin, which prevents clot formation
Eosinophil		Nucleus often bilobed; cytoplasmic granules stain orange-red or bright red; 11–14 µm in diameter	Releases chemicals that reduce inflammation; attacks certain worm parasites
Agranulocytes			
Lymphocyte		Round nucleus; cytoplasm forms a thin ring around the nucleus; 6–14 µm in diameter	Produces antibodies and other chemicals responsible for destroying microorganisms; contributes to allergic reactions, graft rejection, tumor control, and regulation of the immune system
Monocyte		Nucleus round, kidney-shaped, or horseshoe-shaped; contains more cytoplasm than does lymphocyte; 12–20 µm in diameter	Phagocytic cell in the blood; leaves the blood and becomes a macrophage, which phagocytizes bacteria, dead cells, cell fragments, and other debris within tissues
Platelet		Cell fragment surrounded by a plasma membrane and containing granules; 2–4 µm in diameter	Forms platelet plugs; releases chemicals necessary for blood clotting

The formed elements of the blood are outlined and illustrated in table 19.2. In healthy adults, white blood cells are the only formed elements possessing nuclei, whereas red blood cells and platelets lack nuclei.

White blood cells are named according to their appearance in stained preparations. **Granulocytes** (gran′yū-lō-sītz) are white blood cells with large cytoplasmic granules and lobed nuclei (see table 19.2). Their granules stain with dyes that make the cells more visible when viewed through a light microscope. The three types of granulocytes are named according to the staining characteristics of their granules: **neutrophils** (nu′trō-filz) stain with acidic and basic dyes, **eosinophils** (ē-ō-sin′ō-filz) stain with acidic dyes, and **basophils** (bā′sō-filz) stain with basic dyes. **Agranulocytes** (ă-gran′yū-lō-sītz) are white blood cells that appear to have no granules when viewed in the light microscope. Agranulocytes actually have granules, but they are so small that they cannot be seen easily with the light microscope. The two types of agranulocytes are **monocytes** (mon′ō-sītz) and **lymphocytes** (lim′fō-sītz). They have nuclei that are not lobed.

Production of Formed Elements

The process of blood cell production, called **hematopoiesis** (hē′mă-tō-poy-ē′sis, hem´ă-to-poy-ē′sis) or **hemopoiesis** (hē′mō-poy-ē′sis), occurs in the embryo and fetus in tissues like the yolk sac, liver, thymus, spleen, lymph nodes, and red bone marrow. After birth, hematopoiesis is confined primarily to red bone marrow, with some lymphoid tissue helping in the production of lymphocytes (see chapter 22). In young children, nearly all the marrow is red bone marrow. In adults, however, red marrow is confined to the ribs, sternum, vertebrae, pelvis, proximal femur, and proximal humerus. Yellow marrow replaces red marrow in other locations in the body (see chapter 6).

All the formed elements of the blood are derived from a single population of **stem cells** located in the red bone marrow. Hemopoietic stem cells are precursor cells capable of dividing to produce daughter cells that can differentiate into various types of blood cells (figure 19.2): **proerythroblasts** (prō-ĕ-rith′rō-blastz), from which red blood cells develop; **myeloblasts** (mī′ĕ-lō-blastz), from which basophils, eosinophils, and neutrophils develop; **lymphoblasts** (lim′fō-blastz), from which lymphocytes develop; **monoblasts** (mon′ō-blastz), from which monocytes develop; and **megakaryoblasts** (meg-ă-kar′ē-ō-blastz), from which platelets develop. The development of the cell lines is regulated by growth factors. That is, the type of formed element derived from the stem cells and how many formed elements are produced are determined by different growth factors.

3. *Name the three general types of formed elements in the blood.*
4. *Define hematopoiesis. What is a stem cell? What types of formed elements develop from proerythroblasts, myeloblasts, lymphoblasts, monoblasts, and megakaryoblasts?*

Stem Cells and Cancer Therapy

Many cancer therapies affect dividing cells, such as those found in tumors. An undesirable side effect of such therapies, however, can be the destruction of nontumor cells that are dividing, such as the stem cells and their derivatives in red bone marrow. After treatment for cancer, growth factors are used to stimulate the rapid regeneration of the red bone marrow. Although not a cure for cancer, the use of growth factors can speed recovery from the cancer therapy.

Some types of leukemia and genetic immune deficiency diseases can be treated with a bone marrow or stem cell transplant. To avoid problems of tissue rejection, families with a history of these disorders can freeze the umbilical cord blood of their newborn children. The cord blood contains many stem cells and can be used instead of a bone marrow transplant.

Red Blood Cells

Red blood cells, or **erythrocytes,** are about 700 times more numerous than white blood cells and 17 times more numerous than platelets in the blood (figure 19.3*a*). Males have about 5.4 million red blood cells per microliter (μL; 1 mm^3 or 10^{-6} L) of blood (range: 4.6–6.2 million), whereas females have about 4.8 million/μL (range: 4.2–5.4 million). Red blood cells cannot move of their own accord and are passively moved by forces that cause the blood to circulate.

Structure

Normal red blood cells are biconcave disks about 7.5 μm in diameter with edges that are thicker than the center of the cell (figure 19.3*b*). Compared to a flat disk of the same size, the biconcave shape increases the surface area of the red blood cell. The greater surface area makes the movement of gases into and out of the red blood cell more rapid. In addition, the red blood cell can bend or fold around its thin center, thereby decreasing its size and enabling it to pass more easily through small blood vessels.

Red blood cells are derived from specialized cells that lose their nuclei and nearly all their cellular organelles during maturation. The main component of the red blood cell is the pigmented protein **hemoglobin** (hē-mō-glō′bin), which occupies about one-third of the total cell volume and accounts for its red color. Other red blood cell contents include lipids, adenosine triphosphate (ATP), and the enzyme carbonic anhydrase.

Function

The primary functions of red blood cells are to transport oxygen from the lungs to the various tissues of the body and to transport carbon dioxide from the tissues to the lungs. Approximately 98.5% of the oxygen transported in the blood is transported in combination with the hemoglobin in the red blood cells, and the remaining 1.5% is dissolved in the water part of the plasma. If red blood cells rupture, the hemoglobin leaks out into the plasma and becomes nonfunctional because the shape of the molecule changes as a result of denaturation (see chapter 2). Red blood cell rupture followed by hemoglobin release is called **hemolysis** (hē-mol′i-sis).

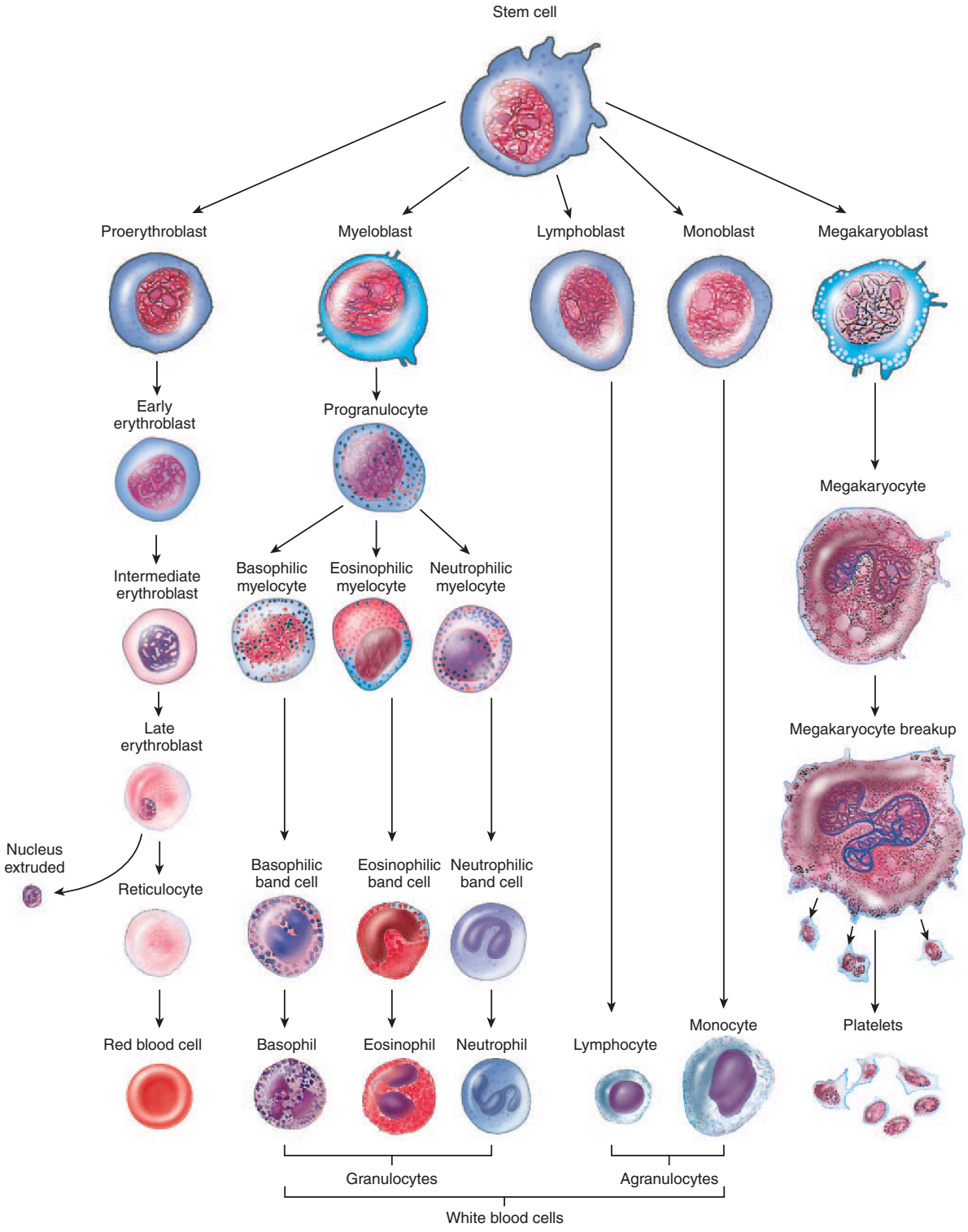


Figure 19.2 Hematopoiesis

Stem cells give rise to the cell lines that produce the formed elements.

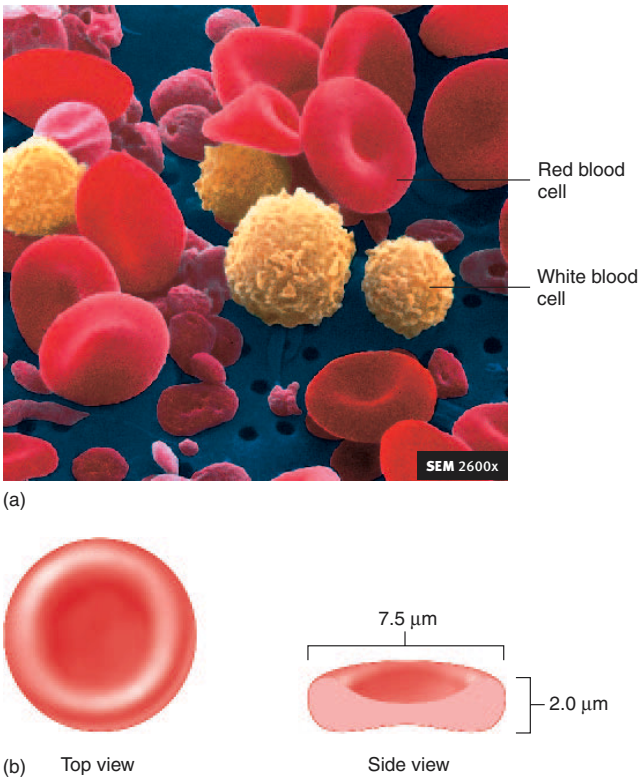


Figure 19.3 Red Blood Cells and White Blood Cells

(*a*) Scanning electron micrograph of formed elements: red blood cells (*red doughnut shapes*) and white blood cells (*yellow*). (*b*) Shape and dimensions of a red blood cell.

Carbon dioxide is transported in the blood in three major ways: approximately 7% is transported as carbon dioxide dissolved in the plasma, approximately 23% is transported in combination with blood proteins (mostly hemoglobin), and 70% is transported in the form of bicarbonate ions. The bicarbonate ions (HCO_3^-) are produced when carbon dioxide (CO_2) and water (H_2O) combine to form carbonic acid (H_2CO_3), which dissociates to form hydrogen (H^+) and bicarbonate ions. The combination of carbon dioxide and water is catalyzed by an enzyme, **carbonic anhydrase,** which is located primarily within red blood cells.

$$\underset{\text{Carbon dioxide}}{CO_2} + \underset{\text{Water}}{H_2O} \overset{\text{Carbonic anhydrase}}{\rightleftarrows} \underset{\text{Carbonic acid}}{H_2CO_3} \rightleftarrows \underset{\text{Hydrogen ion}}{H^+} + \underset{\text{Bicarbonate ion}}{HCO_3^-}$$

Hemoglobin

Hemoglobin consists of four polypeptide chains and four heme groups. Each polypeptide chain, called a **globin** (glō′bin), is bound to one **heme** (hēm). Each heme is a red-pigment molecule containing one **iron atom** (figure 19.4). Several types of globin exist, each having a slightly different amino acid composition. The four globins in normal adult hemoglobin consist of two alpha (α) chains and two beta (β) chains.

Embryonic and fetal hemoglobins appear at different times during development and are replaced by adult hemoglobin near the time of birth. Embryonic and fetal hemoglobins are more effective at binding oxygen than is adult hemoglobin. Abnormal hemoglobins are less effective at attracting oxygen than is normal hemoglobin and can result in anemia (see the Clinical Focus on "Disorders of the Blood" on p. 660).

P R E D I C T 1

What would happen to a fetus if maternal blood had an equal or greater affinity for oxygen than does fetal blood?

Iron is necessary for the normal function of hemoglobin because each oxygen molecule that is transported is associated with an iron atom. The adult human body normally contains about 4 g of iron, two-thirds of which is associated with hemoglobin. Small amounts of iron are regularly lost from the body in waste products like urine and feces. Females lose additional iron as a result of menstrual bleeding and, therefore, require more dietary iron than do males. Dietary iron is absorbed into the circulation from the upper part of the intestinal tract. Stomach acid and vitamin C in food increase the absorption of iron by converting ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), which is more readily absorbed.

Effect of Carbon Monoxide on Oxygen Transport

Various types of poisons affect the hemoglobin molecule. Carbon monoxide (CO), which is produced by the incomplete combustion of gasoline, binds to the iron of hemoglobin to form the relatively stable compound **carboxyhemoglobin** (kar-bok′sē-hē-mō-glō′bin). As a result of the stable binding of carbon monoxide, hemoglobin cannot transport oxygen, and death may occur. Carbon monoxide is found in cigarette smoke, and the blood of smokers can contain 5%–15% carboxyhemoglobin.

When hemoglobin is exposed to oxygen, one oxygen molecule can become associated with each heme group. This oxygenated form of hemoglobin is called **oxyhemoglobin** (ok′sē-hē-mō-glō′bin). Hemoglobin containing no oxygen is called **deoxyhemoglobin.** Oxyhemoglobin is bright red, whereas deoxyhemoglobin has a darker red color.

Hemoglobin also transports carbon dioxide, which doesn't combine with the iron atoms but is attached to amino groups of the globin molecule. This hemoglobin form is **carbaminohemoglobin** (kar-bam′i-nō-hē-mō-glō′bin). The transport of oxygen and carbon dioxide by the blood is discussed more fully in chapter 23.

A recently discovered function of hemoglobin is the transport of nitric oxide, which is produced by the endothelial cells lining blood vessels. In the lungs, at the same time that heme picks up oxygen, in each β-globin a sulfur-containing amino acid, cysteine, binds with a nitric oxide molecule to form *S*-nitrosothiol (nī-trōs′ō-thī-ol; SNO). When oxygen is released in tissues so is the nitric oxide, which functions as a chemical signal that induces the smooth muscle of blood vessels to relax. By affecting the amount of

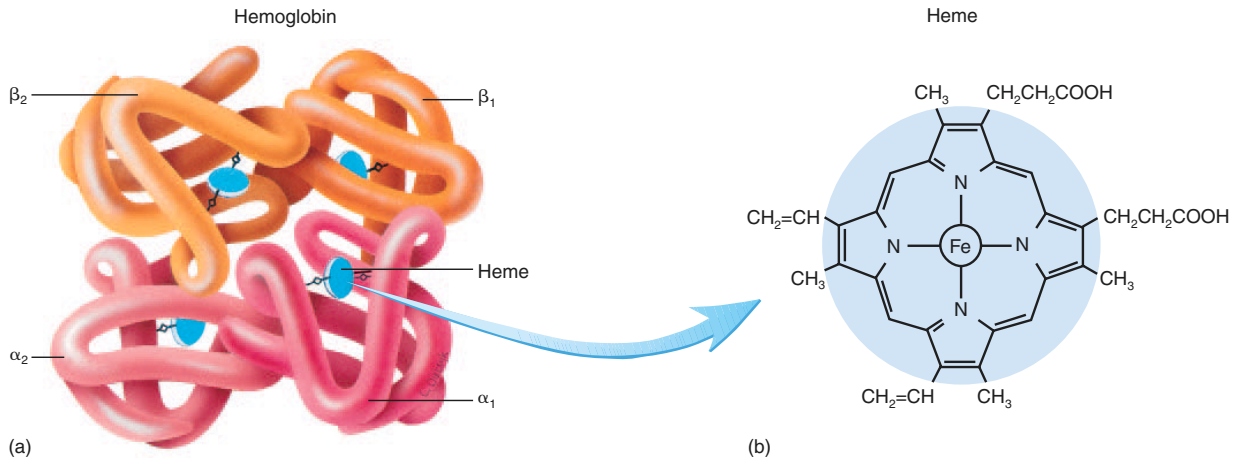


Figure 19.4 Hemoglobin

(*a*) Four polypeptide chains, each with a heme, form a hemoglobin molecule. (*b*) Each heme contains one iron atom.

nitric oxide in tissues, hemoglobin may play a role in regulating blood pressure, because relaxation of blood vessels results in a decrease in blood pressure (see chapter 21).

Blood Substitutes

Current research is being conducted in an attempt to develop blood substitutes that will deliver oxygen to tissues. One such substitute is Hemopure. It is an ultrapurified, chemically cross-linked cow hemoglobin in a balanced salt solution. Thus, Hemopure is a stabilized hemoglobin that is no longer within red blood cells. The use of Hemopure for blood transfusions has several benefits compared to using blood. Hemopure has a longer shelf life than blood and can be used when blood is not available. The free oxygen-carrying hemoglobin molecule of Hemopure is 1000 times smaller than red blood cells, thus allowing it to flow past partially blocked arteries. There are no transfusion reactions because there are no red blood cell surface antigens (see "Blood Grouping" on p. 655). The possibility of transferring human diseases such as hepatitis or AIDS is eliminated. Stringent manufacturing techniques are necessary, however, to ensure the removal of disease-causing agents from cows, such as Creutzfeldt-Jakob disease and bovine spongiform encephalopathy.

Life History of Red Blood Cells

Under normal conditions about 2.5 million red blood cells are destroyed every second. This loss seems staggering until you realize that it represents only 0.00001% of the total 25 trillion red blood cells contained in the normal adult circulation. Furthermore, these 2.5 million red blood cells are replaced by an equal number of red blood cells every second, thus maintaining homeostasis.

The process by which new red blood cells are produced is called **erythropoiesis** (ĕ-rith′rō-poy-ē′sis; see figure 19.2), and the time required for the production of a single red blood cell is about 4 days. Stem cells, from which all blood cells originate, give rise to **proerythroblasts.** After several mitotic divisions, proerythroblasts become **early (basophilic) erythroblasts** (ĕ-rith′rō-blastz), which stain with a basic dye. The dye stains the cytoplasm a purplish color because it binds to the large numbers of ribosomes, which are sites of synthesis for the protein hemoglobin. Early erythroblasts give rise to **intermediate (polychromatic) erythroblasts,** which stain different colors with basic and acidic dyes. As hemoglobin is synthesized and accumulates in the cytoplasm, it's stained a reddish color by an acidic dye. Intermediate erythroblasts continue to produce hemoglobin, and then most of their ribosomes and other organelles degenerate. The resulting **late erythroblasts** have a reddish color because about one-third of the cytoplasm is now hemoglobin.

The late erythroblasts lose their nuclei by a process of extrusion to become immature red blood cells, which are called **reticulocytes** (re-tik′ū-lō-sīts), because a reticulum, or network, can be observed in the cytoplasm when a special staining technique is used. The reticulum is artificially produced by the reaction of the dye with the few remaining ribosomes in the reticulocyte. Reticulocytes are released from the bone marrow into the circulating blood, which normally consists of mature red blood cells and 1%–3% reticulocytes. Within 1 to 2 days, reticulocytes become mature red blood cells when the ribosomes degenerate.

P R E D I C T 2

What does an elevated reticulocyte count indicate? Would the reticulocyte count change during the week after a person had donated a unit (about 500 mL) of blood?

Cell division requires the B vitamins folate and B_{12}, which are necessary for the synthesis of DNA (see chapter 3). Hemoglobin production requires iron. Consequently, adequate amounts of folate, vitamin B_{12}, and iron are necessary for normal red blood cell production.

Red blood cell production is stimulated by low blood oxygen levels, typical causes of which are decreased numbers of red blood cells, decreased or defective hemoglobin, diseases of the lungs, high altitude, inability of the cardiovascular system to deliver blood to tissues, and increased tissue demands for oxygen, for example, during endurance exercises.

Low blood oxygen levels stimulate red blood cell production by increasing the formation of the glycoprotein **erythropoietin** (ĕ-rith-rō-poy′ĕ-tin), which is a hormone produced by the kidneys (figure 19.5). Erythropoietin stimulates red bone marrow to produce more red blood cells by increasing the number of proerythroblasts formed and by decreasing the time required for red blood cells to mature. Thus, when oxygen levels in the blood decrease, erythropoietin production increases, which increases red blood cell production. The increased number of red blood cells increases the ability of the blood to transport oxygen. This mechanism returns blood oxygen levels to normal and maintains homeostasis by increasing the delivery of oxygen to tissues. Conversely, if blood oxygen levels increase, less erythropoietin is released, and red blood cell production decreases.

P R E D I C T 3

Cigarette smoke produces carbon monoxide. If a nonsmoker smoked a pack of cigarettes a day for a few weeks, what would happen to the number of red blood cells in the person's blood? Explain.

Red blood cells normally stay in the circulation for about 120 days in males and 110 days in females. These cells have no nuclei and, therefore, cannot produce new proteins. As their existing proteins, enzymes, plasma membrane components, and other structures degenerate, the red blood cells are less able to transport oxygen and their plasma membranes become more fragile. Eventually the red blood cells rupture as they squeeze through some tight spot in the circulation.

Macrophages located in the spleen, liver, and other lymphatic tissue (figure 19.6) take up the hemoglobin released from ruptured red blood cells. Within the macrophage, lysosomal enzymes digest the hemoglobin to yield amino acids, iron, and bilirubin. The globin part of hemoglobin is broken down into its component amino acids, most of which are reused in the production of other proteins. Iron atoms released from heme can be carried by the blood to red bone marrow, where they are incorporated into new hemoglobin molecules. The heme groups are converted to **biliverdin** (bil-i-ver′din) and then to **bilirubin** (bil-i-roo′bin), which is released into the plasma. Bilirubin binds to albumin and is transported to liver cells. This bilirubin is called **free bilirubin** because it is not yet conjugated. Free bilirubin is taken up by the liver cells and is conjugated, or joined, to glucuronic acid to form **conjugated bilirubin,** which is more water-soluble than free bilirubin. The conjugated bilirubin becomes part of the **bile,** which is the fluid secreted from the liver into the small intestine. In the intestine, bacteria convert bilirubin into the pigments that give feces its characteristic brownish color. Some of these pigments are absorbed from the intestine, modified in the kidneys, and excreted in the urine, thus contributing to the characteristic yellowish color of urine. **Jaundice** (jawn′dis) is a yellowish staining of the skin and sclerae caused by a buildup of bile pigments in the circulation and interstitial spaces.

5. *How does the shape of red blood cells contribute to their ability to exchange gases and move through blood vessels?*
6. *Give the percentage for each of the ways that oxygen and carbon dioxide are transported in the blood. What is the function of carbonic anhydrase?*
7. *Describe the two basic parts of a hemoglobin molecule. Which part is associated with iron? What gases are transported by each part?*

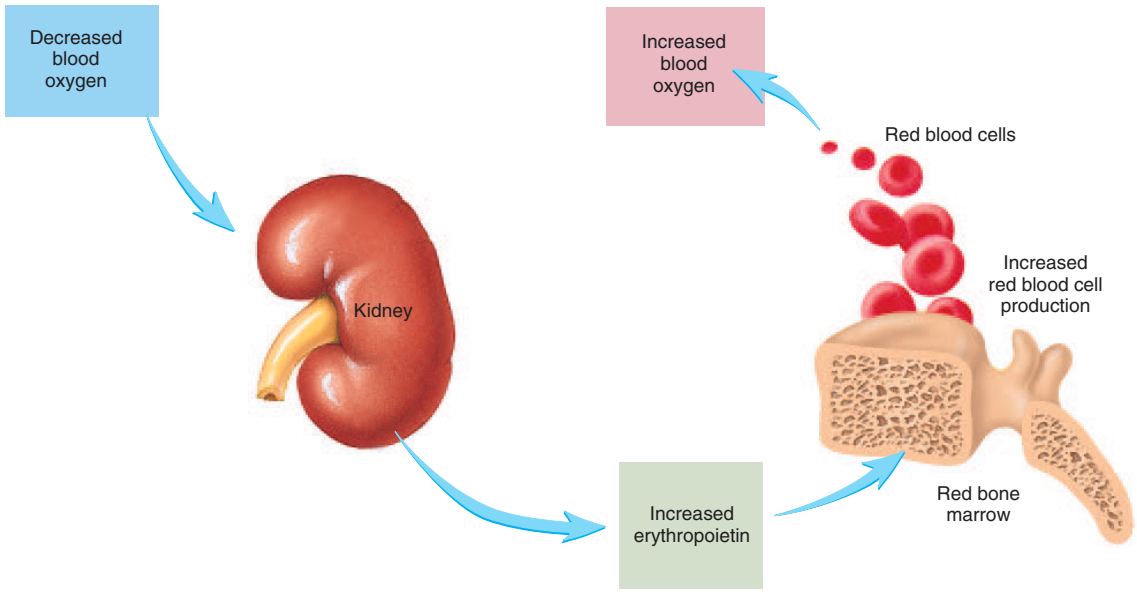
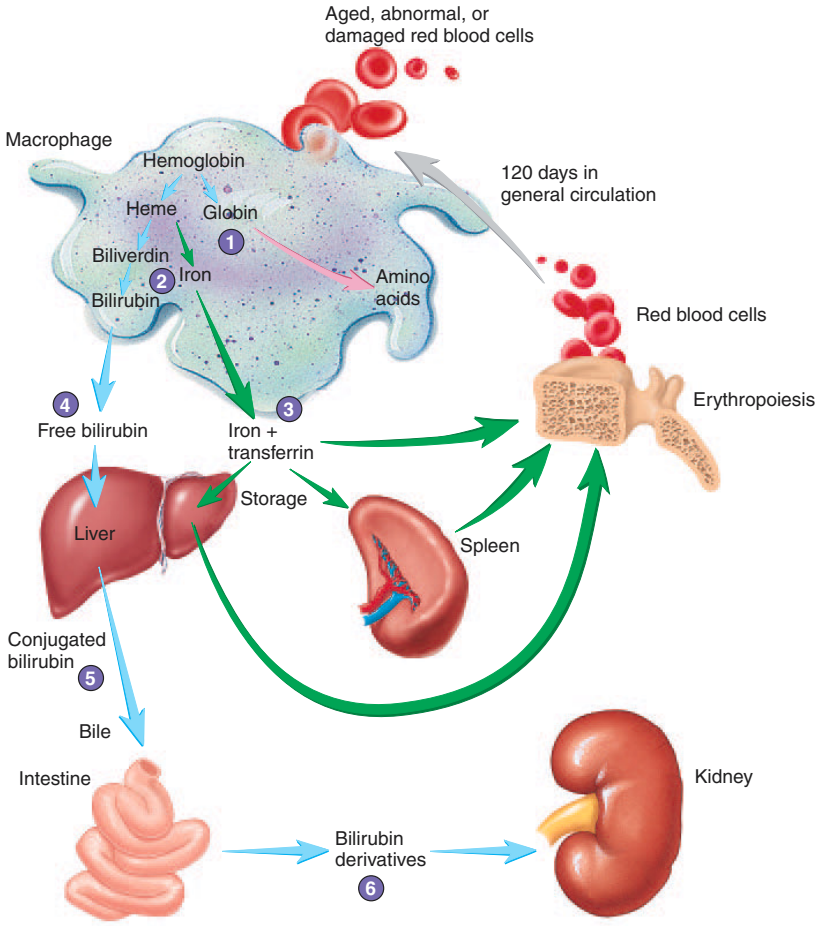


Figure 19.5 Red Blood Cell Production

In response to decreased blood oxygen, the kidneys release erythropoietin into the general circulation. The increased erythropoietin stimulates red blood cell production in the red bone marrow. This process increases blood oxygen levels.

1. The globin chains of hemoglobin are broken down to individual amino acids (*pink arrow*) and are metabolized or used to build new proteins.
2. Iron is released from the heme of hemoglobin. The heme is converted into biliverdin, which is converted into bilirubin.
3. Iron is transported in combination with transferrin in the blood to various tissues for storage or transported to the red bone marrow and used in the production of new hemoglobin (*green arrows*).
4. Free bilirubin (*blue arrow*) is transported in the blood to the liver.
5. Conjugated bilirubin is excreted as part of the bile into the small intestine.
6. Bilirubin derivatives contribute to the color of feces or are reabsorbed from the intestine into the blood and excreted from the kidneys in the urine.



Process Figure 19.6 Hemoglobin Breakdown

Hemoglobin is broken down in macrophages, and the breakdown products are used or excreted.

8. ***Define erythropoiesis. Describe the formation of red blood cells, starting with the stem cells in the red bone marrow.***
9. ***What is erythropoietin, where is it produced, what causes it to be produced, and what effect does it have on red blood cell production?***
10. ***Where are red blood cells removed from the blood? List the three breakdown products of hemoglobin and explain what happens to them.***

White Blood Cells

White blood cells, or **leukocytes,** are clear or whitish-colored cells that lack hemoglobin but have a nucleus. In stained preparations, white blood cells attract stain, whereas red blood cells remain relatively unstained (figure 19.7; see table 19.2).

White blood cells protect the body against invading microorganisms and remove dead cells and debris from the body. Most white blood cells are motile, exhibiting **ameboid movement,** which is the ability to move like an ameba by putting out irregular cytoplasmic projections. White blood cells leave the circulation and enter tissues by **diapedesis** (dī′ă-pĕ-dē′sis), a process in which they become thin and elongated and slip between or, in some cases, through the cells of blood vessel walls. The white blood cells can then be attracted to foreign materials or dead cells within the tissue by **chemotaxis** (kē-mō-tak′sis). At the site of an infection, white blood cells accumulate and phagocytize bacteria, dirt, and dead cells; then they die. The accumulation of dead white blood cells and bacteria, along with fluid and cell debris, is called **pus.**

The five types of white blood cells are neutrophils, eosinophils, basophils, lymphocytes, and monocytes.

Neutrophils

Neutrophils (see table 19.2), the most common type of white blood cells in the blood, have small cytoplasmic granules that stain with both acidic and basic dyes. Their nuclei are commonly lobed, with the number of lobes varying from two to five. Neutrophils are often called **polymorphonuclear** (pol′ē-mōr-fō-noo′klē-ăr) **neutrophils,** or PMNs, to indicate that their nuclei can occur in more than one *(poly)* form *(morph)*. Neutrophils usually remain in the

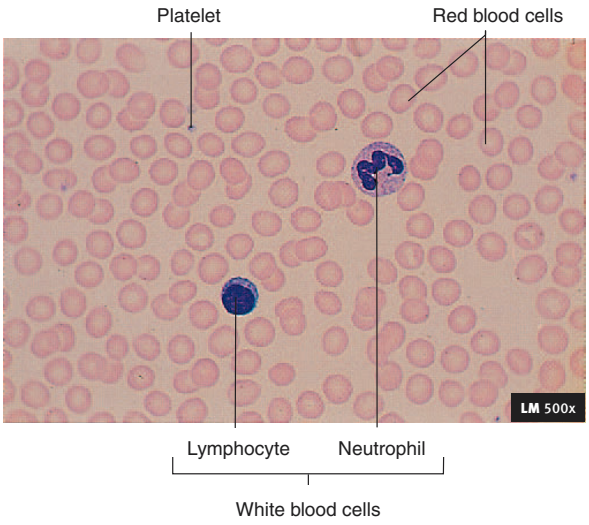


Figure 19.7 Standard Blood Smear

The red blood cells are pink with whitish centers. The centers appear whitish because light more readily shines through the thin center of the disk than through the thicker edges. The white blood cells have been stained and have pink-colored cytoplasm and purple-colored nuclei.

circulation for about 10–12 hours and then move into other tissues, where they become motile and seek out and phagocytize bacteria, antigen–antibody complexes (antigens and antibodies bound together), and other foreign matter. Neutrophils also secrete a class of enzymes called **lysozymes** (lī′sō-zīmz), which are capable of destroying certain bacteria. Neutrophils usually survive for 1–2 days after leaving the circulation.

Eosinophils

Eosinophils (see table 19.2) contain cytoplasmic granules that stain bright red with eosin, an acidic stain. They are motile cells that leave the circulation to enter the tissues during an inflammatory reaction. They are most common in tissues undergoing an allergic response, and their numbers are elevated in the blood of people with allergies. Eosinophils apparently reduce the inflammatory response by producing enzymes that destroy inflammatory chemicals like histamine. Eosinophils also release toxic chemicals that attack certain worm parasites, such as tapeworms, flukes, pinworms, and hookworms.

Basophils

Basophils (see table 19.2), the least common of all white blood cells, contain large cytoplasmic granules that stain blue or purple with basic dyes. Basophils, like eosinophils and neutrophils, leave the circulation and migrate through the tissues, where they play a role in both allergic and inflammatory reactions. Basophils contain large amounts of **histamine,** which they release within tissues to increase inflammation. They also release **heparin,** which inhibits blood clotting.

Lymphocytes

The smallest white blood cells are **lymphocytes,** most of which are slightly larger in diameter than red blood cells (see table 19.2). The lymphocytic cytoplasm consists of only a thin, sometimes imperceptible ring around the nucleus. Although lymphocytes originate in red bone marrow, they migrate through the blood to lymphatic tissues, where they can proliferate and produce more lymphocytes. The majority of the body's total lymphocyte population is in the lymphatic tissues: the lymph nodes, spleen, tonsils, lymphatic nodules, and thymus.

Although they cannot be identified by standard microscopic examination, a number of different kinds of lymphocytes play important roles in immunity (see chapter 22 for details). For example, **B cells** can be stimulated by bacteria or toxins to divide and form cells that produce proteins called **antibodies.** Antibodies can attach to bacteria and activate mechanisms that result in destruction of the bacteria. **T cells** protect against viruses and other intracellular microorganisms by attacking and destroying the cells in which they are found. In addition, T cells are involved in the destruction of tumor cells and tissue graft rejections.

Monocytes

Monocytes are typically the largest of the white blood cells (see table 19.2). They normally remain in the circulation for about 3 days, leave the circulation, become transformed into macrophages, and migrate through various tissues. They phagocytize bacteria, dead cells, cell fragments, and other debris within the tissues. An increase in the number of monocytes is often associated with chronic infections. In addition, macrophages can break down phagocytized foreign substances and present the processed substances to lymphocytes, which results in activation of the lymphocytes (see chapter 22).

11. *What are the two major functions of white blood cells? Define ameboid movement, diapedesis, and chemotaxis.*
12. *Describe the morphology of the five types of white blood cells.*
13. *Name the two white blood cells that function primarily as phagocytic cells. Define lysozymes.*
14. *Which white blood cell reduces the inflammatory response? Which white blood cell releases histamine and promotes inflammation?*
15. *B and T cells are examples of what type of white blood cell? How do these cells protect us against bacteria and viruses?*

P R E D I C T 4

Based on their morphology, identify each of the white blood cells shown in figure 19.8.

Platelets

Platelets, or **thrombocytes** (see figure 19.7 and table 19.2), are minute fragments of cells consisting of a small amount of cytoplasm surrounded by a plasma membrane. Platelets are roughly disk-shaped and average about 3 μm in diameter. The surface of platelets has glycoproteins and proteins that allow platelets to attach to other molecules, for example, collagen in connective tissue.

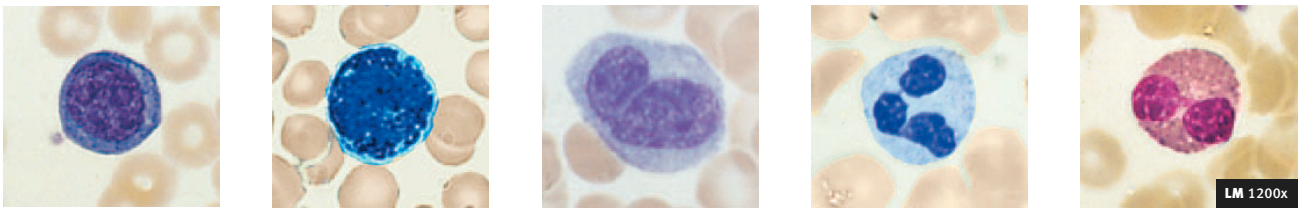


Figure 19.8 Identification of Leukocytes
See Predict question 4.

Some of these surface molecules, as well as molecules released from granules in the platelet cytoplasm, play important roles in controlling blood loss. The platelet cytoplasm also contains actin and myosin, which can cause contraction of the platelet (see section on "Clot Retraction and Dissolution" on p. 654).

The life expectancy of platelets is about 5–9 days. They are produced within the red marrow and are derived from **megakaryocytes** (meg-ă-kar′ē-ō-sītz), which are extremely large cells with diameters up to 100 μm. Small fragments of these cells break off and enter the circulation as platelets.

Platelets play an important role in preventing blood loss by (1) forming platelet plugs, which seal holes in small vessels, and (2) by promoting the formation and contraction of clots, which help seal off larger wounds in the vessels.

16. *What is a platelet? How are platelets formed?*
17. *What are the two major roles of platelets in preventing blood loss?*

Hemostasis

Objectives

- *Describe the stages of hemostasis and clotting.*
- *Give examples of anticoagulants in the blood, and explain their importance.*
- *Describe the processes of clot retraction and dissolution.*

Hemostasis (hē′mō-stā-sis, hē-mos′tă-sis), the arrest of bleeding, is very important to the maintenance of homeostasis. If not stopped, excessive bleeding from a cut or torn blood vessel can result in a positive-feedback cycle, consisting of ever-decreasing blood volume and blood pressure, leading away from homeostasis, and resulting in death. Fortunately, when a blood vessel is damaged, a number of events occur that help prevent excessive blood loss. Vascular spasm, platelet plug formation, and coagulation can cause hemostasis.

Vascular Spasm

Vascular spasm is an immediate but temporary closure of a blood vessel resulting from contraction of smooth muscle within the wall of the vessel. This constriction can close small vessels completely and stop the flow of blood through them. Nervous system reflexes and chemicals produce vascular spasms. For example, during the formation of a platelet plug, platelets release **thromboxanes** (throm′bok-zānz), which are derived from certain prostaglandins, and endothelial cells release the peptide **endothelin** (en-dō′thē-lin).

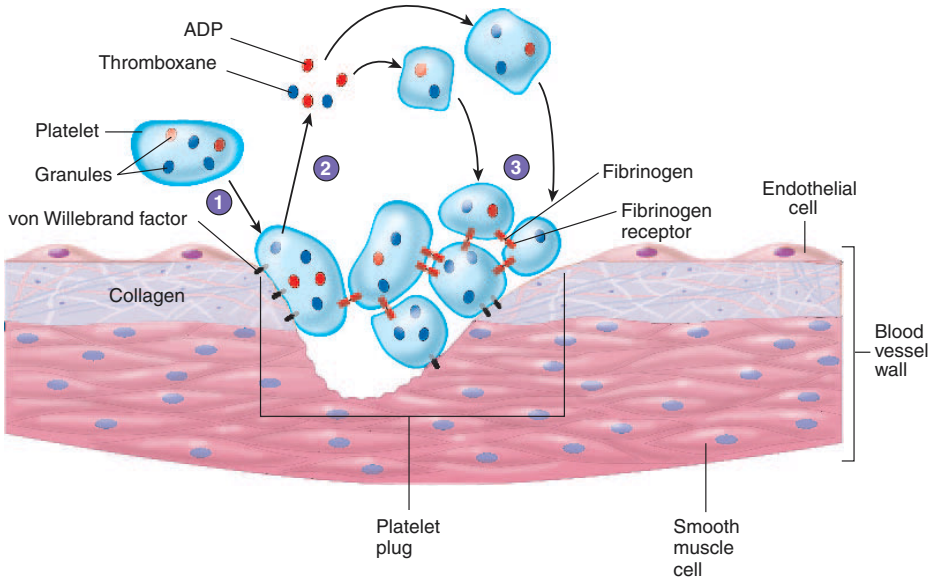
Platelet Plug Formation

A **platelet plug** is an accumulation of platelets that can seal up small breaks in blood vessels. Platelet plug formation is very important in maintaining the integrity of the circulatory system because small tears occur in the smaller vessels and capillaries many times each day, and platelet plug formation quickly closes them. People who lack the normal number of platelets tend to develop numerous small hemorrhages in their skin and internal organs.

The formation of a platelet plug can be described as a series of steps, but in actuality many of the steps take place simultaneously (figure 19.9).

1. **Platelet adhesion** occurs when platelets bind to collagen exposed by blood vessel damage. Most platelet adhesion is mediated through **von Willebrand factor (VWF),** which is a protein produced and secreted by blood vessel endothelial cells. Von Willebrand factor forms a bridge between collagen and platelets by binding to platelet surface receptors and collagen. In addition, other platelet surface receptors can bind directly to collagen.
2. After platelets adhere to collagen, they become activated, and in the **platelet release reaction,** adenosine diphosphate (ADP), thromboxanes, and other chemicals are extruded from the platelets by exocytosis. The ADP and thromboxanes stimulate other platelets to become activated and release additional chemicals, thereby producing a cascade of chemical release by the platelets. Thus, more and more platelets become activated.
3. As platelets become activated, they express surface receptors that can bind to fibrinogen, a plasma protein. In **platelet aggregation,** fibrinogen forms a bridge between the surface receptors of different platelets, resulting in the formation of a platelet plug.
4. Activated platelets express phospholipids (platelet factor III) and coagulation factor V, which are important in clot formation (see following section on "Coagulation").

1. Platelet adhesion occurs when von Willebrand factor connects collagen and platelets.
2. The platelet release reaction is the release of ADP, thromboxanes, and other chemicals that activate other platelets.
3. Platelet aggregation occurs when fibrinogen receptors on activated platelets bind to fibrinogen, connecting the platelets to one another. A platelet plug is formed by the accumulating mass of platelets.



Process Figure 19.9 Platelet Plug Formation

How Aspirin Increases the Risk of Bleeding

Thromboxanes, which activate platelets, are derived from certain prostaglandins. Aspirin inhibits prostaglandin synthesis and, therefore, thromboxane synthesis, which results in reduced platelet activation. If an expectant mother ingests aspirin near the end of pregnancy, prostaglandin synthesis is inhibited and several effects are possible. Two of these effects are (1) the mother can experience excessive postpartum hemorrhage because of decreased platelet function, and (2) the baby can exhibit numerous localized hemorrhages called **petechiae** (pe-tē′kē-ē) over the surface of its body as a result of decreased platelet function. If the quantity of ingested aspirin is large, the infant, mother, or both may die as a result of hemorrhage. On the other hand, in a stroke or heart attack, platelet plugs and clots can form in vessels and threaten the life of the individual. Studies of individuals who are at risk because of the development of clots, such as people who have had a previous heart attack, indicate that taking small amounts of aspirin daily can reduce the likelihood of clot formation and another heart attack. It's not currently recommended, however, that everyone should take aspirin daily.

Coagulation

Vascular spasms and platelet plugs alone are not sufficient to close large tears or cuts. When a blood vessel is severely damaged, **coagulation** (kō-ag-ū-lā′shŭn), or **blood clotting,** results in the formation of a clot. A **blood clot** is a network of threadlike protein fibers, called **fibrin,** that traps blood cells, platelets, and fluid (figure 19.10).

The formation of a blood clot depends on a number of proteins, called **coagulation factors,** found within plasma (table 19.3). Normally the coagulation factors are in an inactive state and don't cause clotting. After injury, the clotting factors are activated to produce a clot. This activation is a complex process involving many chemical reactions, some of which require calcium ions (Ca^{2+}) and molecules on the surface of activated platelets, such as phospholipids and coagulation factor V.

PREDICT 5

Why is it advantageous for clot formation to involve molecules on the surface of activated platelets?

The activation of clotting proteins occurs in three main stages (figure 19.11). **Stage 1** consists of the formation of **prothrombinase, stage 2** is the conversion of **prothrombin** to **thrombin** by prothrombinase, and **stage 3** consists of the conversion of soluble **fibrinogen** to insoluble **fibrin** by thrombin.

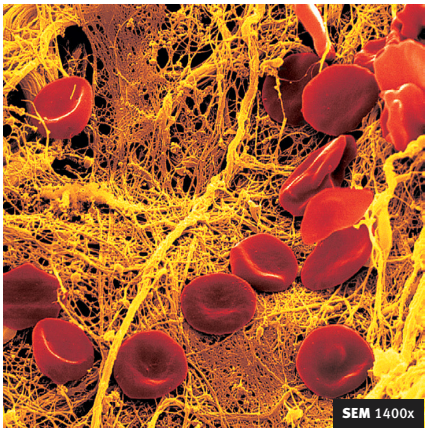


Figure 19.10 Blood Clot

A blood clot consists of fibrin fibers that trap red blood cells, platelets, and fluid.

Table 19.3 Coagulation Factors

Factor Number	Name (synonym)	Description and Function
I	Fibrinogen	Plasma protein synthesized in liver; converted to fibrin in stage 3
II	Prothrombin	Plasma protein synthesized in liver (requires vitamin K); converted to thrombin in stage 2
III	Thromboplastin (tissue factor)	Mixture of lipoproteins released from damaged tissue; required in extrinsic stage 1
IV	Calcium ion	Required throughout entire clotting sequence
V	Proaccelerin (labile factor)	Plasma protein synthesized in liver; activated form functions in stages 1 and 2 of both intrinsic and extrinsic clotting pathways
VI		Once thought to be involved but no longer accepted as playing a role in coagulation; apparently the same as activated factor V
VII	Serum prothrombin conversion accelerator (stable factor, proconvertin)	Plasma protein synthesized in liver (requires vitamin K); functions in extrinsic stage 1
VIII	Antihemophilic factor (antihemophilic globulin)	Plasma protein synthesized in megakaryocytes and endothelial cells; required for intrinsic stage 1
IX	Plasma thromboplastin component (Christmas factor)	Plasma protein synthesized in liver (requires vitamin K); required for intrinsic stage 1
X	Stuart factor (Stuart-Prower factor)	Plasma protein synthesized in liver (requires vitamin K); required in stages 1 and 2 of both intrinsic and extrinsic clotting pathways
XI	Plasma thromboplastin antecedent	Plasma protein synthesized in liver; required for intrinsic stage 1
XII	Hageman factor	Plasma protein required for intrinsic stage 1
XIII	Fibrin-stabilizing factor	Protein found in plasma and platelets; required for stage 3
Platelet Factors		
I	Platelet accelerator	Same as plasma factor V
II	Thrombin accelerator	Accelerates thrombin (intrinsic clotting pathway) and fibrin production
III		Phospholipids necessary for the intrinsic and extrinsic clotting pathways
IV		Binds heparin, which prevents clot formation

Depending on how prothrombinase is formed in stage 1, two separate pathways for coagulation can occur: the **extrinsic clotting pathway** and the **intrinsic clotting pathway.**

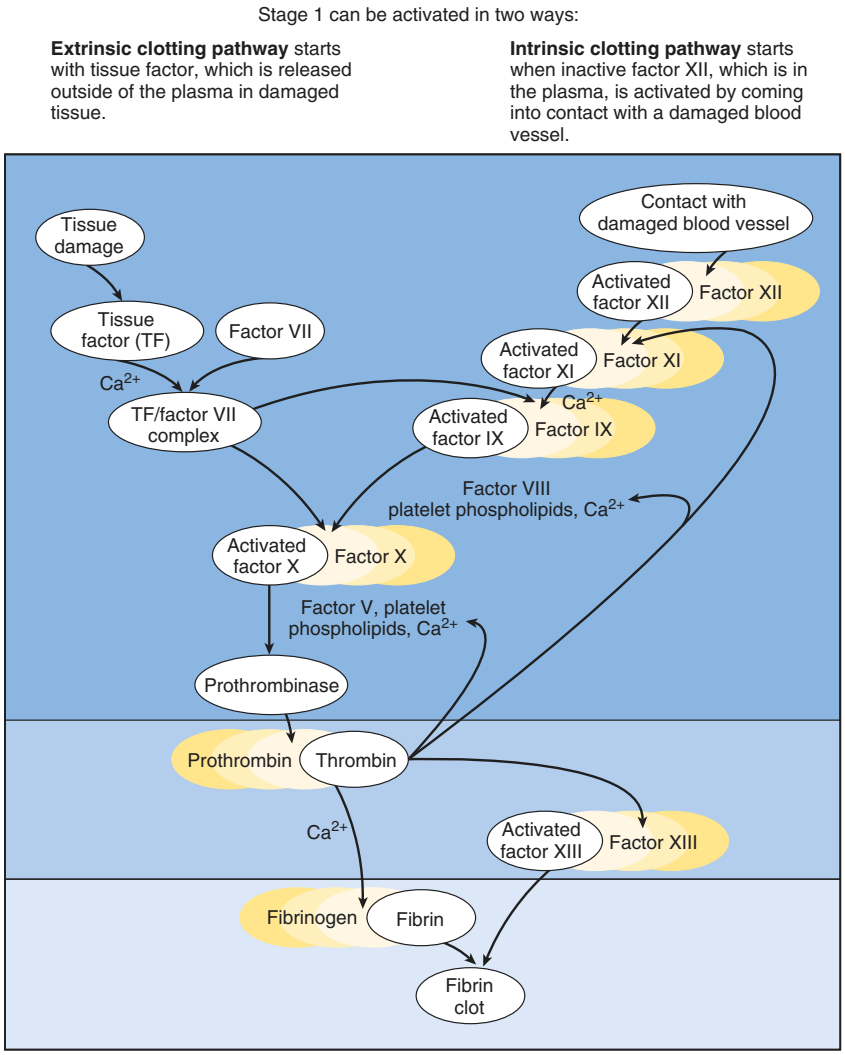
Extrinsic Clotting Pathway

The extrinsic clotting pathway is so named because it begins with chemicals that are outside of, or extrinsic to, the blood (see figure 19.11). In stage 1, damaged tissues release a mixture of lipoproteins and phospholipids called **thromboplastin** (throm-bō-plas′tin), also known as **tissue factor (TF),** or factor III. Thromboplastin, in the presence of Ca^{2+}, forms a complex with factor VII, which activates factor X. On the surface of platelets, activated factor X, factor V, platelet phospholipids, and Ca^{2+} complex to form prothrombinase. In stage 2, prothrombinase converts the soluble plasma protein prothrombin into the enzyme thrombin. During stage 3, thrombin converts the soluble plasma protein fibrinogen into the insoluble protein fibrin. Fibrin forms the fibrous network of the clot. Thrombin also stimulates factor XIII activation, which is necessary to stabilize the clot.

Intrinsic Clotting Pathway

The intrinsic clotting pathway is so named because it begins with chemicals that are inside, or intrinsic to, the blood (see figure 19.11). In stage 1, damage to blood vessels can expose collagen in the connective tissue beneath the epithelium lining the blood vessel. When plasma factor XII comes into contact with collagen, factor XII is activated and it stimulates factor XI, which in turn activates factor IX. Activated factor IX joins with factor VIII, platelet phospholipids, and Ca^{2+} to activate factor X. On the surface of platelets, activated factor X, factor V, platelet phospholipids, and Ca^{2+} complex to form prothrombinase. Stages 2 and 3 then are activated, and a clot results.

Although once considered distinct pathways, it's now known that the extrinsic pathway can activate the clotting proteins in the intrinsic pathway. The TF–VII complex from the extrinsic pathway can stimulate the formation of activated factors IX in the intrinsic pathway. When tissues are damaged, thromboplastin also rapidly leads to the production of thrombin, which can activate many of the clotting proteins such as factor XI and prothrombinase. Thus, thrombin is part of a positive-feedback system in which thrombin production stimulates the production of additional thrombin.



Process Figure 19.11 Clot Formation

Thrombin also has a positive-feedback effect on coagulation by stimulating platelet activation.

18. *What is a vascular spasm? Name two factors that produce it. What is the source of thromboxanes and endothelin?*
19. *What is the function of a platelet plug? Describe the process of platelet plug formation. How are platelets an important part of clot formation?*
20. *What is a clot and what is its function?*
21. *What are coagulation factors?*
22. *Clotting is divided into three stages. Describe the final event that occurs in each stage.*
23. *What is the difference between extrinsic and intrinsic activation of clotting?*

How Vitamin K Helps to Prevent Bleeding

Many of the factors involved in clot formation require vitamin K for their production (see table 19.3). Humans rely on two sources for vitamin K. About half comes from the diet, and half comes from bacteria within the large intestine. Antibiotics taken to fight bacterial infections sometimes kill these intestinal bacteria, thereby reducing vitamin K levels and resulting in bleeding problems. Vitamin K supplements may be necessary for patients on prolonged antibiotic therapy. Newborns lack these intestinal bacteria, and a vitamin K injection is routinely given to infants at birth. Infants can also obtain vitamin K from food such as milk. Because cow's milk contains more vitamin K than does human milk, breast-fed infants are more susceptible to hemorrhage than bottle-fed infants.

The absorption of vitamin K, which is a fat-soluble vitamin, from the intestine requires the presence of bile. Disorders like obstruction of bile flow to the intestine can interfere with vitamin K absorption and lead to insufficient clotting. Liver diseases that result in the decreased synthesis of clotting factors can also lead to insufficient clot formation.

The Danger of Unwanted Clots

When platelets encounter damaged or diseased areas on the walls of blood vessels or the heart, an attached clot called a **thrombus** (throm′bŭs) may form. A thrombus that breaks loose and begins to float through the circulation is called an **embolus** (em′bō-lŭs). Both thrombi and emboli can result in death if they block vessels that supply blood to essential organs, such as the heart, brain, or lungs. Abnormal coagulation can be prevented or hindered by the injection of anticoagulants like heparin, which acts rapidly. Coumadin (koo′mă-din), or warfarin (war′fă-rin), acts more slowly than heparin. Coumadin prevents clot formation by suppressing the production of vitamin K–dependent coagulation factors (II, VII, IX, and X) by the liver. Interestingly, coumadin was first used as a rat poison by causing rats to bleed to death. In small doses, warfarin is a proven, effective anticoagulant in humans. Caution is necessary with anticoagulant treatment, however, because the patient can hemorrhage internally or bleed excessively when cut.

Control of Clot Formation

Without control, coagulation would spread from the point of initiation to the entire circulatory system. Furthermore, vessels in a healthy person contain rough areas that can stimulate clot formation, and small amounts of prothrombin are constantly being converted into thrombin. To prevent unwanted clotting, the blood contains several **anticoagulants** (an′tē-kō-ag′ū-lantz), which prevent coagulation factors from initiating clot formation. Only when coagulation factor concentrations exceed a given threshold does coagulation occur. At the site of injury, so many coagulation factors are activated that the anticoagulants are unable to prevent clot formation. Away from the injury site, however, the activated coagulation factors are diluted in the blood, anticoagulants neutralize them, and clotting is prevented.

Examples of anticoagulants in the blood are antithrombin, heparin, and prostacyclin. **Antithrombin,** a plasma protein produced by the liver, slowly inactivates thrombin. **Heparin,** produced by basophils and endothelial cells, increases the effectiveness of antithrombin because heparin and antithrombin together rapidly inactivate thrombin. **Prostacyclin** (pros-tă-sī′klin) is a prostaglandin derivative produced by endothelial cells. It counteracts the effects of thrombin by causing vasodilation and by inhibiting the release of coagulation factors from platelets.

Anticoagulants are also important when blood is outside the body. They prevent the clotting of blood used in transfusions and laboratory blood tests. Examples include heparin, **ethylenediaminetetraacetic** (eth′il-ēn-dī′ă-mēn-tet-ră-ă-sē′tik) **acid (EDTA),** and sodium citrate. EDTA and sodium citrate prevent clot formation by binding to Ca^{2+}, thus making the ions inaccessible for clotting reactions.

Clot Retraction and Dissolution

The fibrin meshwork constituting the clot adheres to the walls of the blood vessel. Once a clot has formed, it begins to condense into a denser, compact structure through a process known as **clot retraction.** Platelets contain the contractile proteins actin and myosin, which operate in a similar fashion to that of actin and myosin in smooth muscle (see chapter 9). Platelets form small extensions that attach to fibrin. Contraction of the extensions pulls on the fibrin and is responsible for clot retraction. As the clot condenses, a fluid called **serum** (sēr′ŭm) is squeezed out of it. Serum is plasma from which fibrinogen and some of the clotting factors have been removed.

Consolidation of the clot pulls the edges of the damaged blood vessel together, which can help to stop the flow of blood, reduce infection, and enhance healing. The damaged vessel is repaired by the movement of fibroblasts into the damaged area and the formation of new connective tissue. In addition, epithelial cells around the wound proliferate and fill in the torn area.

The clot usually is dissolved within a few days after clot formation by a process called **fibrinolysis** (fī-bri-nol′i-sis), which involves the activity of **plasmin** (plaz′min), an enzyme that hydrolyzes fibrin. Plasmin is formed from inactive plasminogen, which is a normal blood protein. It's activated by thrombin, factor XII, tissue plasminogen activator (t-PA), urokinase, and lysosomal enzymes released from damaged tissues (figure 19.12). In disorders that are caused by blockage of a vessel by a clot, such as a heart attack, dissolving the clot can restore blood flow and reduce damage to tissues. For example, streptokinase (a bacterial enzyme), t-PA, or urokinase can be injected into the blood or introduced at the clot site by means of a catheter. These substances convert plasminogen to plasmin, which breaks down the clot.

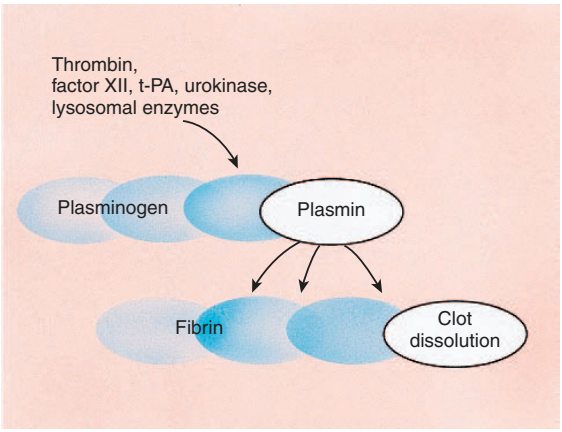


Figure 19.12 Fibrinolysis

Plasminogen is converted by thrombin, factor XII, tissue plasminogen activator (t-PA), urokinase, or lysosomal enzymes to the active enzyme plasmin. Plasmin breaks the fibrin molecules and therefore the clot into smaller pieces, which are washed away in the blood or are phagocytized.

24. *What is the function of anticoagulants in blood? Name three anticoagulants in blood, and explain how they prevent clot formation.*
25. *Define the terms thrombus and embolus, and explain why they are dangerous.*
26. *Describe clot retraction. What is serum?*
27. *What is fibrinolysis? How does it occur?*

Blood Grouping

Objective

- *Explain the basis of ABO and Rh incompatibilities.*

If large quantities of blood are lost during surgery or in an accident, the patient can go into shock and die unless a transfusion or infusion is performed. A **transfusion** is the transfer of blood or blood components from one individual to another. When large quantities of blood are lost, red blood cells must be replaced so that the oxygen-carrying capacity of the blood is restored. An **infusion** is the introduction of a fluid other than blood, such as a saline or glucose solution, into the blood. In many cases, the return of blood volume to normal levels is all that is necessary to prevent shock. Eventually, the body produces red blood cells to replace those that were lost.

Early attempts to transfuse blood from one person to another were often unsuccessful because they resulted in transfusion reactions, which included clotting within blood vessels, kidney damage, and death. It's now known that transfusion reactions are caused by interactions between antigens and antibodies (see chapter 22). In brief, the surfaces of red blood cells have molecules called **antigens** (an′ti-jenz), and, in the plasma, molecules called **antibodies** are present. Antibodies are very specific, meaning that each antibody can combine only with a certain antigen. When the antibodies in the plasma bind to the antigens on the surfaces of the red blood cells, they form molecular bridges that connect the red blood cells. As a result, **agglutination** (ă-gloo-ti-nā′shŭn), or clumping, of the cells occurs. The combination of the antibodies with the antigens can also initiate reactions that cause **hemolysis,** or rupture of the red blood cells. Because the antigen–antibody combinations can cause agglutination, the antigens are often called **agglutinogens** (ă-gloo-tin′ō-jenz), and the antibodies are called **agglutinins** (ă-gloo′ti-ninz).

The antigens on the surface of red blood cells have been categorized into **blood groups,** and more than 35 blood groups, most of which are rare, have been identified. For transfusions, the ABO and Rh blood groups are among the most important. Other well-known groups include the Lewis, Duffy, MNSs, Kidd, Kell, and Lutheran groups.

ABO Blood Group

In the **ABO blood group,** type A blood has type A antigens, type B blood has type B antigens, type AB blood has both types of antigens, and type O blood has neither A nor B antigens on the surface of red blood cells (figure 19.13). In addition, plasma from type A blood contains anti-B antibodies, which act against type B antigens, whereas plasma from type B blood contains anti-A antibodies, which act against type A antigens. Type AB blood has neither type of antibody, and type O blood has both anti-A and anti-B antibodies.

The ABO blood types are not found in equal numbers. In Caucasians in the United States, the distribution is type O, 47%; type A, 41%; type B, 9%; and type AB, 3%. Among African-Americans, the distribution is type O, 46%; type A, 27%; type B, 20%; and type AB, 7%.

Antibodies normally don't develop against an antigen unless the body is exposed to that antigen. This means, for example, that a person with type A blood should not have anti-B antibodies unless he or she has received a transfusion of type B blood, which contains type B antigens. People with type A blood do have anti-B antibodies, however, even though they have never received a transfusion of type B blood. One possible explanation is that type A or B antigens on bacteria or food in the digestive tract stimulate the formation of antibodies against antigens that are different from one's own antigens. Thus a person with type A blood would produce anti-B antibodies against the B antigens on the bacteria or food. In support of this hypothesis is the observation that anti-A and anti-B antibodies are not found in the blood until about 2 months after birth.

A blood **donor** gives blood, and a **recipient** receives blood. Usually a donor can give blood to a recipient if they both have the same blood type. For example, a person with type A blood could donate to another person with type A blood. No ABO transfusion reaction would occur because the recipient has no anti-A antibodies against the type A antigen. On the other hand, if type A blood were donated to a person with type B blood, a transfusion reaction would occur because the person with type B blood has anti-A antibodies against the type A antigen, and agglutination would result (figure 19.14).

Historically, people with type O blood have been called universal donors because they usually can give blood to the other ABO blood types without causing an ABO transfusion reaction. Their red blood cells have no ABO surface antigens and, therefore, do not react

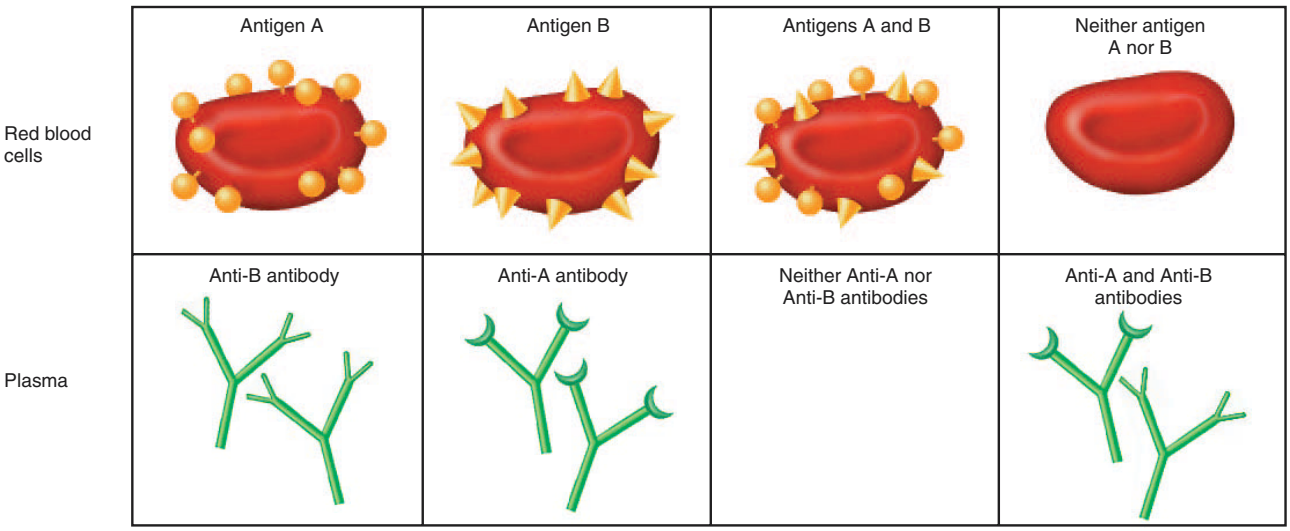


Figure 19.13 ABO Blood Groups

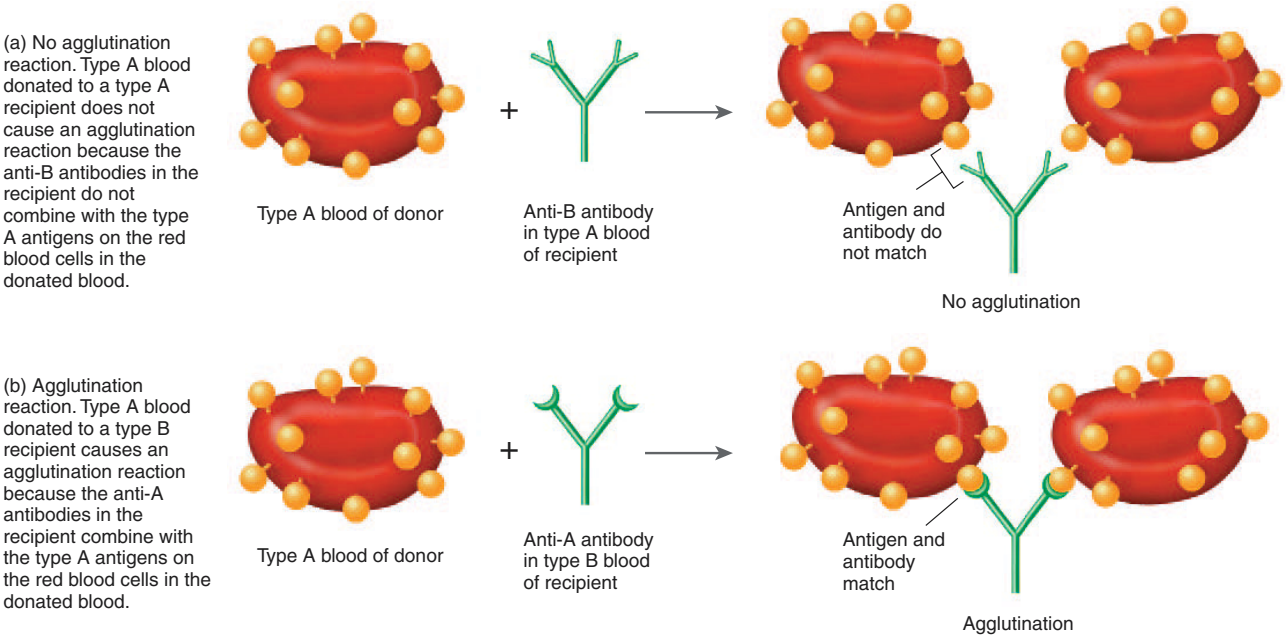


Figure 19.14 Agglutination Reaction

with the recipient's anti-A or anti-B antibodies. For example, if type O blood is given to a person with type A blood, the type O red blood cells do not react with the anti-B antibodies in the recipient's blood. In a similar fashion, if type O blood is given to a person with type B blood, no reaction occurs to the recipient's anti-A antibodies.

The term *universal donor* is misleading, however. Transfusion of type O blood, in some cases, produces a transfusion reaction for two reasons. First, other blood groups can cause a transfusion reaction. Second, antibodies in the blood of the donor can react with antigens in the blood of the recipient. For example, type O blood has anti-A and anti-B antibodies. If type O blood is transfused into a person with type A blood, the anti-A antibodies (in the type O blood) react against the A antigens (in the type A blood). Usually such reactions are not serious because the antibodies in the donor's blood are diluted in the blood of the recipient, and few reactions take place. Because type O blood sometimes causes transfusion reactions, it's given to a person with another blood type only in life-or-death emergency situations.

28. *What are blood groups, and how do they cause transfusion reactions? Define the terms agglutination and hemolysis.*
29. *What kinds of antigens and antibodies are found in each of the four ABO blood types?*
30. *Why is a person with type O blood considered to be a universal donor?*

PREDICT 6

Historically, people with type AB blood were called universal recipients. What is the rationale for this term? Explain why the term is misleading.

Rh Blood Group

Another important blood group is the **Rh blood group,** so named because it was first studied in rhesus monkeys. People are Rh-positive if they have certain Rh antigens (the D antigens) on the surface of their red blood cells, and people are Rh-negative if they do not have these Rh antigens. About 85% of Caucasians in the United States and 88% of African-Americans are Rh-positive. The ABO blood type and the Rh blood type usually are designated together. For example, a person designated as A positive is type A in the ABO blood group and Rh-positive. The rarest combination in the United States is AB negative, which occurs in less than 1% of all Americans.

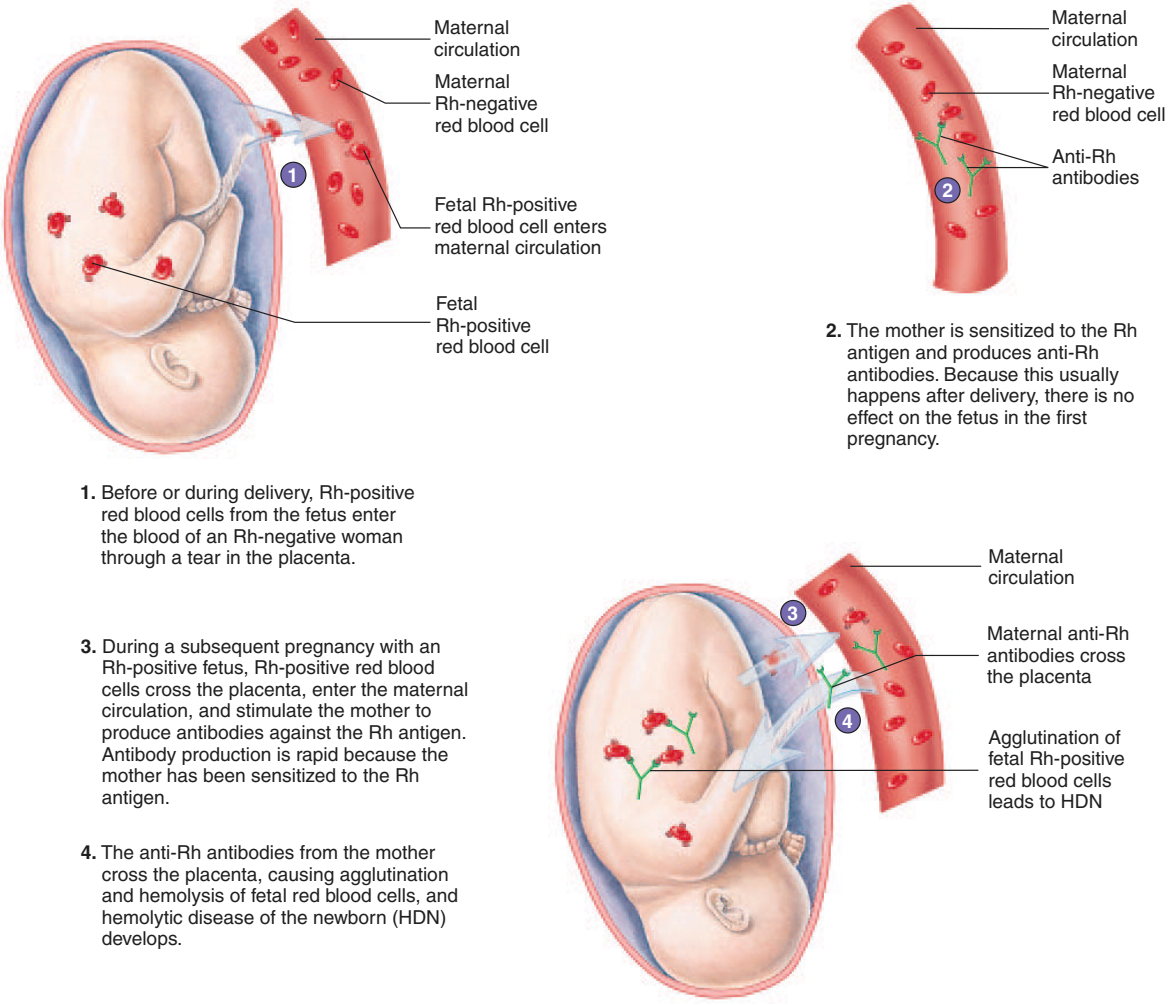
Antibodies against the Rh antigen do not develop unless an Rh-negative person is exposed to Rh-positive blood. This can occur through a transfusion or by transfer of blood between a mother and her fetus across the placenta. When an Rh-negative person receives a transfusion of Rh-positive blood, the recipient becomes sensitized to the Rh antigen and produces anti-Rh antibodies. If the Rh-negative person is unfortunate enough to receive a second transfusion of Rh-positive blood after becoming sensitized, a transfusion reaction results.

Rh incompatibility can pose a major problem in some pregnancies when the mother is Rh-negative and the fetus is Rh-positive (figure 19.15). If fetal blood leaks through the placenta and mixes with the mother's blood, the mother becomes sensitized to the Rh antigen. The mother produces anti-Rh antibodies that cross the placenta and cause agglutination and hemolysis of fetal red blood cells. This disorder is called **hemolytic disease of the newborn (HDN),** or **erythroblastosis fetalis** (ĕ-rith′rō-blas-tō′sis fē-ta′lis), and it may be fatal to the fetus. In the woman's first pregnancy, however, usually no problem occurs. The leakage of fetal blood is usually the result of a tear in the placenta that takes place either late in the pregnancy or during delivery. Thus, not enough time exists for the mother to produce enough anti-Rh antibodies to harm the fetus. In later pregnancies, however, a problem can arise because the mother has already been sensitized to the Rh antigen. Consequently, if the fetus is Rh-positive and if any leakage of fetal blood into the mother's blood occurs, she rapidly produces large amounts of anti-Rh antibodies, and HDN develops.

HDN can be prevented if the Rh-negative woman is given an injection of a specific type of antibody preparation, called Rh_0(D) immune globulin (RhoGAM). The injection can be administered during the pregnancy or before or immediately after each delivery or abortion. The injection contains antibodies against Rh antigens. The injected antibodies bind to the Rh antigens of any fetal red blood cells that may have entered the mother's blood. This treatment inactivates the fetal Rh antigens and prevents sensitization of the mother.

If HDN develops, treatment consists of slowly removing the newborn's blood and replacing it with Rh-negative blood. The newborn can also be exposed to fluorescent light, because the light helps to break down the large amounts of bilirubin formed as a result of red blood cell destruction. High levels of bilirubin are toxic to the nervous system and can damage brain tissue.

31. *What is meant by the term Rh-positive?*
32. *What Rh blood types must the mother and fetus have before HDN can occur?*
33. *How is HDN harmful to the fetus?*
34. *Why doesn't HDN usually develop in the first pregnancy?*
35. *How can HDN be prevented? How is HDN treated?*



Process Figure 19.15 Hemolytic Disease of the Newborn (HDN)

Diagnostic Blood Tests

Objective

- ***Describe diagnostic blood tests and the normal values for the tests. Give examples of disorders that produce abnormal test results.***

Type and Crossmatch

To prevent transfusion reactions the blood is typed, and a **crossmatch** is made. **Blood typing** determines the ABO and Rh blood groups of the blood sample. Typically, the cells are separated from the serum. The cells are tested with known antibodies to determine the type of antigen on the cell surface. For example, if a patient's blood cells agglutinate when mixed with anti-A antibodies but do not agglutinate when mixed with anti-B antibodies, it's concluded that the cells have type A antigen. In a similar fashion, the serum is mixed with known cell types (antigens) to determine the type of antibodies in the serum.

Normally, donor blood must match the ABO and Rh type of the recipient. Because other blood groups can also cause a transfusion reaction, however, a crossmatch is performed. In a crossmatch, the donor's blood cells are mixed with the recipient's serum, and the donor's serum is mixed with the recipient's cells. The donor's blood is considered safe for transfusion only if no agglutination occurs in either match.

Complete Blood Count

The **complete blood count (CBC)** is an analysis of the blood that provides much information. It consists of a red blood count, hemoglobin and hematocrit measurements, a white blood count, and a differential white blood count.

Red Blood Count

Blood cell counts usually are done automatically with an electronic instrument, but they can also be done manually with a microscope. The normal range for a **red blood count (RBC)** is the number

(expressed in millions) of red blood cells per microliter of blood. It is 4.6–6.2 million/μL of blood for a male, and 4.2–5.4 million/μL of blood for a female. **Erythrocytosis** (ĕ-rith′rō-sī-tō′sis) is an overabundance of red blood cells. It can result from a decreased oxygen supply, which stimulates erythropoietin secretion by the kidney, or from red bone marrow tumors. Because red blood cells tend to stick to one another, increasing the number of red blood cells makes it more difficult for blood to flow. Consequently, erythrocytosis increases the workload of the heart. It also can reduce blood flow through tissues and, if severe, can result in plugging of small blood vessels (capillaries).

Hemoglobin Measurement

The **hemoglobin measurement** determines the amount of hemoglobin in a given volume of blood, usually expressed as grams of hemoglobin per 100 mL of blood. The normal hemoglobin count for a male is 14–18 g/100 mL of blood, and for a female it is 12–16 g/100 mL of blood. Abnormally low hemoglobin is an indication of **anemia** (ă-nē′mē-ă), which is a reduced number of red blood cells per 100 mL of blood or a reduced amount of hemoglobin in each red blood cell.

Hematocrit Measurement

The percentage of total blood volume composed of red blood cells is the **hematocrit** (hē′mă-tō-krit, hem′ă-tō -krit). One way to determine hematocrit is to place blood in a tube and spin the tube in a centrifuge. The formed elements are heavier than the plasma and are forced to one end of the tube (figure 19.16). White blood cells and platelets form a thin, whitish layer, called the **buffy coat,** between the plasma and the red blood cells. The red blood cells account for 40%–54% of the total blood volume in males and 38%–47% in females.

The number and size of red blood cells affect the hematocrit measurement. **Normocytes** (nōr′mō-sītz) are normal sized red blood cells with a diameter of 7.5 μm. **Microcytes** (mī′krō-sītz) are smaller than normal with a diameter of 6 μm or less, and **macrocytes** (mak′krō-sītz) are larger than normal with a diameter 9 μm or greater. Blood disorders can result in abnormal hematocrit measurement because they cause red blood cells numbers to be abnormally high or low, or cause red blood cells to be abnormally small or large (see "Disorders of the Blood" on p. 660). A decreased hematocrit indicates that the volume of red blood cells is less than normal. It can result from a decreased number of normocytes or a normal number of microcytes. For example, inadequate iron in the diet can impair hemoglobin production. Consequently, during their formation red blood cells do not fill with hemoglobin, and they remain smaller than normal.

White Blood Count

A **white blood count (WBC)** measures the total number of white blood cells in the blood. Normally 5000–10,000 white blood cells are present in each microliter of blood. **Leukopenia** (loo-kō-pē′nē-ă) is a lower-than-normal WBC and can indicate depression or destruction of the red marrow by radiation, drugs, tumor, or a deficiency of vitamin B_{12} or folate. **Leukocytosis** (loo′kō-sī-tō′sis) is an abnormally high WBC. **Leukemia** (loo-kē′mē-ă) (a cancer of the red marrow) often results in leukocytosis, but the white blood cells have an abnormal structure and function. Bacterial infections also can cause leukocytosis.

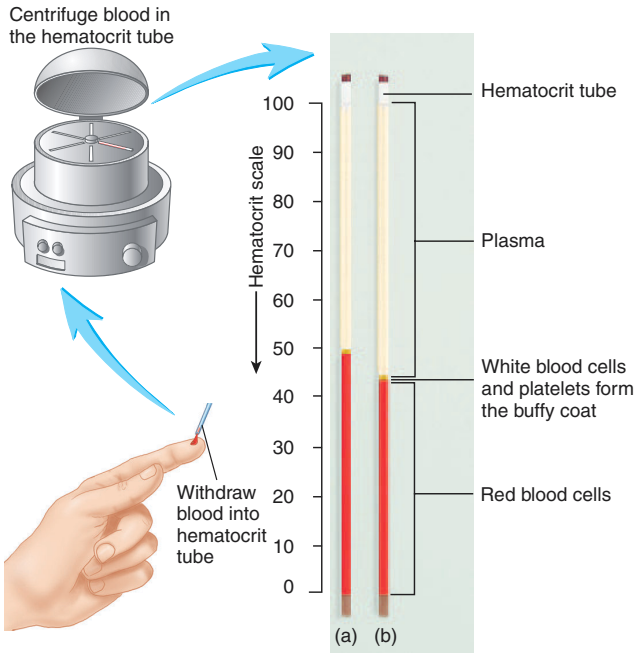


Figure 19.16 Hematocrit

Blood is withdrawn into a capillary tube and placed in a centrifuge. The blood is separated into plasma, red blood cells, and a small amount of white blood cells and platelets, which rest on the red blood cells. The hematocrit measurement is the percent of the blood volume that is red blood cells. It doesn't measure the white blood cells and platelets. Normal hematocrits for a male (*a*) and a female (*b*) are shown.

Differential White Blood Count

A **differential white blood count** determines the percentage of each of the five kinds of white blood cells in the WBC. Normally neutrophils account for 60%–70%; lymphocytes, 20%–30%; monocytes, 2%–8%; eosinophils, 1%–4%; and basophils, 0.5%–1%. A differential WBC can provide much insight about a patient's condition. For example, in patients with bacterial infections the neutrophil count is often greatly increased, whereas in patients with allergic reactions the eosinophil and basophil counts are elevated.

Clotting

Two measurements that test the ability of the blood to clot are the platelet count and prothrombin time.

Platelet Count

A normal **platelet count** is 250,000–400,000 platelets per microliter of blood. **Thrombocytopenia** (throm′bō-sī-tō-pē′nē-ă) is a condition in which the platelet count is greatly reduced, resulting in chronic bleeding through small vessels and capillaries. It can be caused by decreased platelet production as a result of hereditary disorders, lack of vitamin B_{12}, drug therapy, or radiation therapy.

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Clinical Focus Disorders of the Blood

Erythrocytosis

Erythrocytosis (ĕ-rith′rō-sī-tō′sis) is an overabundance of red blood cells, resulting in increased blood viscosity, reduced flow rates, and, if severe, plugging of the capillaries. **Relative erythrocytosis** results from decreased plasma volume, such as that caused by dehydration, diuretics, and burns. **Primary erythrocytosis,** often called **polycythemia vera** (pol′ē-sī-thē′mē-ă ve′ra), is a stem cell defect of unknown cause that results in the overproduction of red blood cells, granulocytes, and platelets. Erythropoietin levels are low and the spleen can be enlarged. **Secondary erythrocytosis (polycythemia)** results from a decreased oxygen supply, such as that which occurs at high altitudes, in chronic obstructive pulmonary disease, or in congestive heart failure. The resulting decrease in oxygen delivery to the kidneys stimulates erythropoietin secretion and causes an increase in red blood cell production. In both types of polycythemia the increased number of red blood cells increases blood viscosity and blood volume. There can be clogging of capillaries and the development of hypertension.

Anemia

Anemia (ă-nē′mē-ă) is a deficiency of hemoglobin in the blood. It can result from a decrease in the number of red blood cells, a decrease in the amount of hemoglobin in each red blood cell, or both. The decreased hemoglobin reduces the ability of the blood to transport oxygen. Anemic patients suffer from a lack of energy and feel excessively tired and listless. They can appear pale and quickly become short of breath with only slight exertion.

One general cause of anemia is nutritional deficiencies. **Iron-deficiency anemia** results from a deficient intake or absorption of iron or from excessive iron loss. Consequently, not enough hemoglobin is produced, and the red blood cells are smaller than normal (microcytic). **Folate deficiency** can also cause anemia. An inadequate amount of folate in the diet is the usual cause of folate deficiency, with the disorder developing most often in the poor, in pregnant women, and in chronic alcoholics. Because folate helps in the synthesis of DNA, folate deficiency results in fewer cell divisions. There is decreased red blood cell production, but the cells grow larger than normal (macrocytic). Another type of nutritional anemia is **pernicious** (per-nish′ŭs) **anemia,** which is caused by inadequate amounts of vitamin B_{12}. Because vitamin B_{12} is important for folate synthesis, inadequate amounts of it can also result in the decreased production of red blood cells that are larger than normal. Although inadequate levels of vitamin B_{12} in the diet can cause pernicious anemia, the usual cause is insufficient absorption of the vitamin. Normally the stomach produces intrinsic factor, a protein that binds to vitamin B_{12}. The combined molecules pass into the small intestine, where intrinsic factor facilitates the absorption of the vitamin. Without adequate levels of intrinsic factor, insufficient vitamin B_{12} is absorbed, and pernicious anemia develops. Present evidence suggests that the inability to produce intrinsic factor is due to an autoimmune disease in which the body's immune system damages the cells in the stomach that produce intrinsic factor.

Another general cause of anemia is loss or destruction of red blood cells. **Hemorrhagic** (hem-ŏ-raj′ik) **anemia** results from a loss of blood, such as can result from trauma, ulcers, or excessive menstrual bleeding. Chronic blood loss, in which small amounts of blood are lost over time, can result in iron-deficiency anemia. **Hemolytic** (hē-mō-lit′ik) **anemia** is a disorder in which red blood cells rupture or are destroyed at an excessive rate. It can be caused by inherited defects within the red blood cells. For example, one kind of inherited hemolytic anemia results from a defect in the plasma membrane that causes red blood cells to rupture easily. Many kinds of hemolytic anemia result from unusual damage to the red blood cells by drugs, snake venom, artificial heart valves, autoimmune disease, or hemolytic disease of the newborn.

Aplastic anemia is caused by an inability of the red bone marrow to produce normal red blood cells (normocytic). It's usually acquired as a result of damage to the red marrow by chemicals (e.g., benzene), drugs (e.g., certain antibiotics and sedatives), or radiation.

Some anemias result from inadequate or defective hemoglobin production. **Thalassemia** (thal-ă-sē′mē-ă) is a hereditary disease found predominantly in people of Mediterranean, Asian, and African ancestry. It's caused by insufficient production of the globin part of the hemoglobin molecule. The major form of the disease results in death by age 20, the minor form in a mild anemia. **Sickle-cell disease** is a hereditary disease found mostly in people of African ancestry but also occasionally among people of Mediterranean heritage. It results in the formation of an abnormal hemoglobin, in which the red blood cells assume a rigid sickle shape and plug up small blood vessels (figure A). They are also more fragile than normal red blood cells. In its severe form, sickle-cell disease is usually fatal before the person is 30 years of age, whereas in its minor form, sickle-cell trait, symptoms usually do not occur.

Von Willebrand's Disease

Von Willebrand's disease is the most common inherited bleeding disorder; it occurs as frequently as 1 in 1000 individuals. Von Willebrand factor (vWF) helps platelets to stick to collagen (platelet adhesion) and is the plasma carrier for factor VIII (see discussion on "Coagulation" on p. 651 and table 19.3). One treatment for von

Figure A Sickle-Cell Disease

Red blood cells in a person with sickle-cell disease appear normal in oxygenated blood. In deoxygenated blood, hemoglobin changes shape and causes the cells to become sickle-shaped and rigid.

Willebrand's disease involves injections of vWF or concentrates of factor VIII to which vWF is attached. Another therapeutic approach is to administer a drug that increases vWF levels in the blood.

Hemophilia

Hemophilia (hē-mō-fil′ē-ă) is a genetic disorder in which clotting is abnormal or absent. It's most often found in people from northern Europe and their descendants. Because hemophilia is an X-linked trait (see chapter 29), it occurs almost exclusively in males. **Hemophilia A** (classic hemophilia) results from a deficiency of plasma coagulation factor VIII, and **hemophilia B** is caused by a deficiency in plasma factor IX. Hemophilia A occurs in approximately 1 in 10,000 male births, and hemophilia B occurs in approximately 1 in 100,000 male births. Treatment of hemophilia involves injection of the missing clotting factor taken from donated blood.

Thrombocytopenia

Thrombocytopenia (throm′bō-sī-tō-pē′nē-ă) is a condition in which the number of platelets is greatly reduced, resulting in chronic bleeding through small vessels and capillaries. Thrombocytopenia has several causes, including increased platelet destruction, caused by autoimmune disease (see chapter 22) or infections, and decreased platelet production, resulting from hereditary disorders, pernicious anemia, drug therapy, radiation therapy, or leukemias.

Leukemia

The leukemias are cancers of the red bone marrow in which abnormal production of one or more of the white blood cell types occur. Because these cells are usually immature or abnormal and lack their normal immunologic functions, patients are very susceptible to infections. The excess production of white blood cells in the red marrow can also interfere with red blood cell and platelet formation and thus lead to anemia and bleeding.

Infectious Diseases of the Blood

Microorganisms don't normally survive in the blood. Blood can transport microorganisms, however, and they can multiply in the blood. Microorganisms can enter the body and be transported by the blood to the tissues they infect. For example, the poliomyelitis virus enters through the gastrointestinal tract and is carried to nervous tissue. After microorganisms are established at a site of infection, some can enter the blood. They can then be transported to other locations in the body, multiply within the blood, or be eliminated by the body's immune system.

Septicemia (sep-ti-sē′mē-ă), or blood poisoning, is the spread of microorganisms and their toxins by the blood. Often septicemia results from the introduction of microorganisms by a medical procedure, such as the insertion of an intravenous tube into a blood vessel. The release of toxins by microorganisms can cause septic shock, which is a decrease in blood pressure that can result in death.

In a few diseases, microorganisms actually multiply within blood cells. **Malaria** (mă-lār′ē-ă) is caused by a protozoan *(Plasmodium)* that is introduced into the blood by the bite of the *Anopheles* mosquito. Part of the development of the protozoan occurs inside red blood cells. The symptoms of chills and fever in malaria are produced by toxins released when the protozoan causes the red blood cells to rupture. **Infectious mononucleosis** (mon′ō-noo-klē-ō′sis) is caused by a virus (Epstein-Barr virus) that infects lymphocytes (B cells). The lymphocytes are altered by the virus, and the immune system attacks and destroys the lymphocytes. The immune system response is believed to produce the symptoms of fever, sore throat, and swollen lymph nodes. **Acquired immunodeficiency syndrome (AIDS)** is caused by the human immunodeficiency virus (HIV), which infects lymphocytes and suppresses the immune system (see chapter 22).

The presence of microorganisms in the blood is a concern with blood transfusions, because it's possible to infect the blood recipient. Blood is routinely tested, especially for AIDS and hepatitis, in an effort to eliminate this risk. **Hepatitis** (hep-ă-tī′tis) is an infection of the liver caused by several kinds of viruses. After recovering, hepatitis victims can become carriers. Although they show no signs of the disease, they release the virus into their blood or bile. To prevent infection of others, anyone who has had hepatitis is asked not to donate blood products.

Prothrombin Time Measurement

Prothrombin time measurement is a measure of how long it takes for the blood to start clotting, which normally is 9–12 seconds. Prothrombin time is determined by adding thromboplastin to whole plasma. Thromboplastin is a chemical released from injured tissues that starts the process of clotting (see figure 19.11). Prothrombin time is officially reported as the International Normalized Ratio (INR), which standardizes the time it takes to clot based on the slightly different thromboplastins used by different labs. Because many clotting factors must be activated to form prothrombin, a deficiency of any one of them can cause an abnormal prothrombin time. Vitamin K deficiency, certain liver diseases, and drug therapy can cause an increased prothrombin time.

Blood Chemistry

The composition of materials dissolved or suspended in the plasma can be used to assess the functioning of many of the body's systems (Appendix E). For example, high blood glucose levels can indicate that the pancreas is not producing enough insulin; high blood urea nitrogen (BUN) can be a sign of reduced kidney function; increased bilirubin can indicate liver dysfunction or hemolysis; and high cholesterol levels can indicate an increased risk of developing cardiovascular disease. A number of blood chemistry tests are routinely done when a blood sample is taken, and additional tests are available.

36. For each of the following tests, define the test and give an example of a disorder that would cause an abnormal test result:
- *a. red blood count*
- *b. hemoglobin measurement*
- *c. hematocrit measurement*
- *d. white blood count*
- *e. differential white blood count*
- *f. platelet count*
- *g. prothrombin time measurement*
- *h. blood chemistry tests*

PREDICT 7

When a patient complains of acute pain in the abdomen, the physician suspects appendicitis, which is often caused by a bacterial infection of the appendix. What blood test should be done to support the diagnosis?

SUMMARY

Functions of Blood (p. 640)

1. Blood transports gases, nutrients, waste products, and hormones.
2. Blood is involved in the regulation of homeostasis and the maintenance of pH, body temperature, fluid balance, and electrolyte levels.
3. Blood protects against disease and blood loss.

Plasma (p. 641)

1. Plasma is mostly water (91%) and contains proteins, such as albumin (maintains osmotic pressure), globulins (function in transport and immunity), fibrinogen (involved in clot formation), and hormones and enzymes (involved in regulation).
2. Plasma also contains ions, nutrients, waste products, and gases.

Formed Elements (p. 642)

The formed elements include red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (cell fragments).

Production of Formed Elements

1. In the embryo and fetus, the formed elements are produced in a number of locations.
2. After birth, red bone marrow becomes the source of the formed elements.
3. All formed elements are derived from stem cells.

Red Blood Cells

1. Red blood cells are biconcave disks containing hemoglobin and carbonic anhydrase.
   - A hemoglobin molecule consists of four heme and four globin molecules. The heme molecules transport oxygen, and the globin molecules transport carbon dioxide and nitric oxide. Iron is required for oxygen transport.
   - Carbonic anhydrase is involved with the transport of carbon dioxide.
2. Erythropoiesis is the production of red blood cells.
   - Stem cells in red bone marrow eventually give rise to late erythroblasts, which lose their nuclei and are released into the blood as reticulocytes. Loss of the endoplasmic reticulum by a reticulocyte produces a red blood cell.
   - In response to low blood oxygen, the kidneys produce erythropoietin, which stimulates erythropoiesis.
3. Hemoglobin from ruptured red blood cells is phagocytized by macrophages. The hemoglobin is broken down, and heme becomes bilirubin, which is secreted in bile.

White Blood Cells

1. White blood cells protect the body against microorganisms and remove dead cells and debris.
2. Five types of white blood cells exist.
   - Neutrophils are small phagocytic cells.
   - Eosinophils function to reduce inflammation.
   - Basophils release histamine and are involved with increasing the inflammatory response.
   - Lymphocytes are important in immunity, including the production of antibodies.
   - Monocytes leave the blood, enter tissues, and become large phagocytic cells called macrophages.

Platelets

Platelets, or thrombocytes, are cell fragments pinched off from megakaryocytes in the red bone marrow.

Hemostasis (p. 650)

Hemostasis is very important to the maintenance of homeostasis.

Vascular Spasm

Vasoconstriction of damaged blood vessels reduces blood loss.

Platelet Plug Formation

1. Platelets repair minor damage to blood vessels by forming platelet plugs.
   - In platelet adhesion, platelets bind to collagen in damaged tissues.
   - In the platelet release reaction, platelets release chemicals that activate additional platelets.
   - In platelet aggregation, platelets bind to one another to form a platelet plug.
2. Platelets also release chemicals involved with coagulation.

Coagulation

1. Coagulation is the formation of a blood clot.
2. Coagulation consists of three stages.
   - Activation of prothrombinase.
   - Conversion of prothrombin to thrombin by prothrombinase.
   - Conversion of fibrinogen to fibrin by thrombin. The insoluble fibrin forms the clot.
3. The first stage of coagulation occurs through the extrinsic or intrinsic clotting pathway. Both pathways end with the production of prothrombinase.
   - The extrinsic clotting pathway begins with the release of thromboplastin from damaged tissues.
   - The intrinsic clotting pathway begins with the activation of factor XII.

Control of Clot Formation

1. Heparin and antithrombin inhibit thrombin activity. Fibrinogen is, therefore, not converted to fibrin, and clot formation is inhibited.
2. Prostacyclin counteracts the effects of thrombin.

Clot Retraction and Dissolution

1. Clot retraction results from the contraction of platelets, which pull the edges of damaged tissue closer together.
2. Serum, which is plasma minus fibrinogen and some clotting factors, is squeezed out of the clot.
3. Factor XII, thrombin, tissue plasminogen activator, and urokinase activate plasmin, which dissolves fibrin (the clot).

Blood Grouping (p. 655)

1. Blood groups are determined by antigens on the surface of red blood cells.
2. Antibodies can bind to red blood cell antigens, resulting in agglutination or hemolysis of red blood cells.

ABO Blood Group

1. Type A blood has A antigens, type B blood has B antigens, type AB blood has A and B antigens, and type O blood has neither A nor B antigens.
2. Type A blood has anti-B antibodies, type B blood has anti-A antibodies, type AB blood has neither anti-A nor anti-B antibodies, and type O blood has both anti-A and anti-B antibodies.
3. Mismatching the ABO blood group results in transfusion reactions.

Rh Blood Group

1. Rh-positive blood has certain Rh antigens (the D antigens), whereas Rh-negative blood does not.
2. Antibodies against the Rh antigen are produced by an Rh-negative person when the person is exposed to Rh-positive blood.
3. The Rh blood group is responsible for hemolytic disease of the newborn.

Diagnostic Blood Tests (p. 658)

Type and Crossmatch

Blood typing determines the ABO and Rh blood groups of a blood sample. A crossmatch tests for agglutination reactions between donor and recipient blood.

Complete Blood Count

The complete blood count consists of the following: red blood count, hemoglobin measurement (grams of hemoglobin per 100 mL of blood), hematocrit measurement (percent volume of red blood cells), and white blood count.

Differential White Blood Count

The differential white blood count determines the percentage of each type of white blood cell.

Clotting

Platelet count and prothrombin time measure the ability of the blood to clot.

Blood Chemistry

The composition of materials dissolved or suspended in plasma (e.g., glucose, urea nitrogen, bilirubin, and cholesterol) can be used to assess the functioning and status of the body's systems.

REVIEW AND COMPREHENSION

1. Which of these is a function of blood?
   a. clot formation
   b. protection against foreign substances
   c. maintenance of body temperature
   d. regulation of pH and osmosis
   e. all of the above
2. Which of these is *not* a component of plasma?
   a. nitrogen
   b. sodium ions
   c. platelets
   d. water
   e. urea
3. Which of these plasma proteins plays an important role in maintaining the osmotic concentration of the blood?
   a. albumin
   b. fibrinogen
   c. platelets
   d. hemoglobin
   e. globulins
4. The cells that give rise to the red blood cells are
   a. lymphoblasts.
   b. megakaryoblasts.
   c. monoblasts.
   d. myeloblasts.
   e. proerythroblasts.

5. Red blood cells
   a. are the least numerous formed element in the blood.
   b. are phagocytic cells.
   c. are produced in the yellow marrow.
   d. do not have a nucleus.
   e. all of the above.
6. Given these ways of transporting carbon dioxide in the blood:
   1. bicarbonate ions
   2. combined with blood proteins
   3. dissolved in plasma

   Choose the arrangement that lists them in the correct order from largest to smallest percentage of carbon dioxide transported.
   a. 1, 2, 3
   b. 1, 3, 2
   c. 2, 3, 1
   d. 2, 1, 3
   e. 3, 1, 2
7. Which of these components of a red blood cell is correctly matched with its function?
   a. heme group of hemoglobin—oxygen transport
   b. globin portion of hemoglobin—carbon dioxide transport
   c. carbonic anhydrase—carbon dioxide transport
   d. cysteine on β-globin—nitric oxide transport
   e. all of the above
8. Each hemoglobin molecule can become associated with _____ oxygen molecules.
   a. one
   b. two
   c. three
   d. four
   e. unlimited
9. Which of these substances is *not* required for normal red blood cell production?
   a. folate
   b. vitamin K
   c. iron
   d. vitamin B_{12}
10. Erythropoietin
    a. is produced mainly by the heart.
    b. inhibits the production of red blood cells.
    c. production increases when blood oxygen decreases.
    d. production is inhibited by testosterone.
    e. all of the above.
11. Which of these changes occurs in the blood in response to the initiation of a vigorous exercise program?
    a. increased erythropoietin production
    b. increased concentration of reticulocytes
    c. decreased bilirubin formation
    d. both a and b
    e. all of the above
12. Which of the components of hemoglobin is correctly matched with its fate following the destruction of a red blood cell?
    a. heme: reused to form a new hemoglobin molecule
    b. globin: broken down into amino acids
    c. iron: mostly secreted in bile
    d. all of the above
13. If you live near sea level and are training for a track meet in Denver (5280 ft elevation), you would want to spend a few weeks before the meet training at
    a. sea level.
    b. an altitude similar to Denver's.
    c. a facility with a hyperbaric chamber.
    d. any location—it doesn't matter.
14. The blood cells that function to inhibit inflammation are
    a. eosinophils.
    b. basophils.
    c. neutrophils.
    d. monocytes.
    e. lymphocytes.
15. The most numerous type of white blood cell, whose primary function is phagocytosis, is
    a. eosinophils.
    b. basophils.
    c. neutrophils.
    d. monocytes.
    e. lymphocytes.
16. Monocytes
    a. are the smallest white blood cells.
    b. increase in number during chronic infections.
    c. give rise to neutrophils.
    d. produce antibodies.
17. The white blood cells that release large amounts of histamine and heparin are
    a. eosinophils.
    b. basophils.
    c. neutrophils.
    d. monocytes.
    e. lymphocytes.
18. The smallest white blood cells, which include B cells and T cells, are
    a. eosinophils.
    b. basophils.
    c. neutrophils.
    d. monocytes.
    e. lymphocytes.
19. Platelets
    a. are derived from megakaryocytes.
    b. are cell fragments.
    c. have surface molecules that attach to collagen.
    d. play an important role in clot formation.
    e. all of the above.
20. Given these processes in platelet plug formation:
    1. platelet adhesion
    2. platelet aggregation
    3. platelet release reaction

    Choose the arrangement that lists the processes in the correct order after a blood vessel is damaged.
    a. 1, 2, 3
    b. 1, 3, 2
    c. 3, 1, 2
    d. 3, 2, 1
    e. 2, 3, 1
21. A constituent of blood plasma that forms the network of fibers in a clot is
    a. fibrinogen.
    b. tissue factor.
    c. platelets.
    d. thrombin.
    e. prothrombinase.
22. Given these chemicals:
    1. activated factor XII
    2. fibrinogen
    3. prothrombinase
    4. thrombin

Choose the arrangement that lists the chemicals in the order they are used during clot formation.
a. 1, 3, 4, 2
b. 2, 3, 4, 1
c. 3, 2, 1, 4
d. 3, 1, 2, 4
e. 3, 4, 2, 1

23. The extrinsic clotting pathway
a. begins with the release of thromboplastin (tissue factor).
b. leads to the production of prothrombinase.
c. requires Ca^{2+}.
d. all of the above.

24. Which of these is *not* an anticoagulant found in the blood?
a. ethylenediamenetetraacetic acid (EDTA)
b. antithrombin
c. heparin
d. prostacyclin

25. The chemical that is involved in the breakdown of a clot (fibrinolysis) is
a. antithrombin.
b. fibrinogen.
c. heparin.
d. plasmin.
e. sodium citrate.

26. A person with type A blood
a. has anti-A antibodies.
b. has type B antigens.
c. will have a transfusion reaction if given type B blood.
d. all of the above.

27. In the United States, the most common blood type is
a. A positive.
b. B positive.
c. O positive.
d. O negative.
e. AB negative.

28. Rh-negative mothers who receive a RhoGAM injection are given that injection to
a. initiate the synthesis of anti-Rh antibodies in the mother.
b. initiate anti-Rh antibody production in the baby.
c. prevent the mother from producing anti-Rh antibodies.
d. prevent the baby from producing anti-Rh antibodies.

29. The blood test that distinguishes between leukocytosis and leukopenia is
a. type and crossmatch.
b. hematocrit.
c. platelet count.
d. complete blood count.
e. prothrombin time measurement.

30. An elevated neutrophil count is usually indicative of
a. an allergic reaction.
b. a bacterial infection.
c. a viral infection.
d. a parasitic infection.
e. increased antibody production.

Answers in Appendix F

CRITICAL THINKING

1. In hereditary hemolytic anemia, massive destruction of red blood cells occurs. Would you expect the reticulocyte count to be above or below normal? Explain why one of the symptoms of the disease is jaundice. In 1910, it was discovered that hereditary hemolytic anemia could be successfully treated by removing the spleen. Explain why this treatment is effective.
2. Red Packer, a physical education major, wanted to improve his performance in an upcoming marathon race. About 6 weeks before the race, 500 mL of blood was removed from his body, and the formed elements were separated from the plasma. The formed elements were frozen, and the plasma was reinfused into his body. Just before the competition, the formed elements were thawed and injected into his body. Explain why this procedure, called blood doping or blood boosting, would help Red's performance. Can you suggest any possible bad effects?
3. Chemicals like benzene and chloramphenicol can destroy red bone marrow and cause aplastic anemia. What symptoms develop as a result of the lack of (a) red blood cells, (b) platelets, and (c) white blood cells?
4. Some people habitually use barbiturates to depress feelings of anxiety. Barbiturates cause hypoventilation, which is a slower-than-normal rate of breathing, because they suppress the respiratory centers in the brain. What happens to the red blood count of a habitual user of barbiturates? Explain.
5. What blood problems would you expect to observe in a patient after total gastrectomy (removal of the stomach)? Explain.
6. According to the old saying, "Good food makes good blood." Name three substances in the diet that are essential for "good blood." What blood disorders develop if these substances are absent from the diet?

Answers in Appendix G

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ANSWERS TO PREDICT QUESTIONS

1. The reason fetal hemoglobin must be more effective at binding oxygen than adult hemoglobin is so that the fetal circulation can draw the needed oxygen away from the maternal circulation. If maternal blood had an equal or greater oxygen affinity, the fetal blood would not be able to draw away the required oxygen, and the fetus would die.
2. An elevated reticulocyte count indicates that erythropoiesis and the demand for red blood cells are increased and that immature red blood cells (reticulocytes) are entering the circulation in large numbers. An elevated reticulocyte count can occur for a number of reasons, including loss of blood; therefore, after a person donates a unit of blood, the reticulocyte count increases.
3. Carbon monoxide binds to the iron of hemoglobin and prevents the transport of oxygen. The decreased oxygen stimulates the release of erythropoietin, which increases red blood cell production in red bone marrow, thereby causing the number of red blood cells in the blood to increase.
4. The white blood cells shown in figure 19.8 are (a) lymphocyte, (b) basophil, (c) monocyte, (d) neutrophil, and (e) eosinophil.
5. Platelets become activated at sites of tissue damage, which is the location where it's advantageous to form a clot to stop bleeding.
6. People with type AB blood were called universal recipients because they could receive type A, B, AB, or O blood with little likelihood of a transfusion reaction. Type AB blood does not have antibodies against type A or B antigens; therefore, transfusion of these antigens in type A, B, or AB blood does not cause a transfusion reaction in a person with type AB blood. The term is misleading, however, for two reasons. First, other blood groups can cause a transfusion reaction. Second, antibodies in the donor's blood can cause a transfusion reaction. For example, type O blood contains anti-A and anti-B antibodies that can react against the A and B antigens in type AB blood.
7. A white blood count (WBC) should be done. An elevated WBC, leukocytosis, can be an indication of bacterial infections. A differential WBC should also be done. An increase in the number of neutrophils supports the diagnosis of a bacterial infection. Coupled with other symptoms, this could mean appendicitis. If these tests are normal, appendicitis is still a possibility and the physician must rely on other clinical signs. Diagnostic accuracy for appendicitis is approximately 75%–85% for experienced physicians.

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