Blood has always had a special mystique. From time immemorial, people have seen blood flow from the body and with it, the life of the individual. People thus presumed that blood carried a mysterious "vital force," and Roman gladiators drank it to fortify themselves for battle. Even today, we become especially alarmed when we find ourselves bleeding, and the emotional impact of blood is enough to make many people faint at the sight of it. From ancient Egypt to nineteenth-century America, physicians drained "bad blood" from their patients to treat everything from gout to headaches, from menstrual cramps to mental illness. It was long thought that hereditary traits were transmitted through the blood, and people still use such unfounded expressions as "I have one-quarter Cherokee blood."

Scarcely anything meaningful was known about blood until blood cells were seen with the first microscopes. Even though blood is a uniquely accessible tissue, most of what we know about it dates only to the last 50 years. Recent developments in **hematology**[1]—the study of blood—have empowered us to save and improve the lives of countless people who would otherwise suffer or die.

Table 18.1 Functions of the Blood

Transport

Carries O_2 and CO_2 between the lungs and other organs

Carries nutrients from the digestive system and storage depots to other organs

Carries wastes to the liver and kidneys for detoxification or removal

Carries hormones from endocrine glands to target cells

Carries heat to the skin for removal; helps regulate body temperature

Protection

Plays several roles in inflammation

Leukocytes destroy microorganisms and cancer cells

Antibodies and other proteins neutralize or destroy pathogens

Platelet factors initiate clotting and minimize blood loss

Regulation

Transfers water to and from the tissues; helps stabilize water balance

Buffers acids and bases; helps stabilize pH

Functions and Properties of Blood

Objectives

When you have completed this section, you should be able to

- state the various functions of blood;
- list the components of blood;
- explain why the viscosity and osmolarity of blood are important; and
- state what components account for its viscosity and osmolarity.

The blood plays more roles than one might expect (table 18.1); it is involved in respiration, nutrition, waste elimination, thermoregulation, immune defense, water and acid-base balance, and internal communication. Most adults have 4 to 6 L of blood. It is a connective tissue with two main components—the **plasma,** a clear extracellular fluid, and the **formed elements,** which consist of the blood cells and platelets (fig. 18.1).

The formed elements are classified as follows. They are called *formed elements* because they are enclosed in a plasma membrane and have a definite shape and visible structure. All of them are cells except for the platelets, which are fragments of certain bone marrow cells.

Erythrocytes
Platelets
Leukocytes
  Granulocytes
    Neutrophils
    Eosinophils
    Basophils
  Agranulocytes
    Lymphocytes
    Monocytes

Erythrocytes[2] (eh-RITH-ro-sites) are also known as *red blood cells (RBCs)* and leukocytes[3] (LOO-co-sites) are also known as *white blood cells (WBCs).*

The formed elements can be separated from the plasma by placing a sample of blood in a tube and spinning it for a few minutes in a centrifuge (fig. 18.2). RBCs, being more dense than the blood plasma, become packed into the bottom of the tube and typically constitute about 45% of the total volume. This value is called the *hematocrit.* WBCs and platelets make up a narrow cream-colored zone called the *buffy coat* just above the RBCs. At the top of the tube is the plasma, which has a pale yellow color and accounts for nearly 55% of the total volume.

Table 18.2 lists several properties of blood. Its viscosity and osmolarity warrant special attention. **Viscosity** is the resistance of a fluid to flow due to cohesion between its particles. At a given temperature, mineral oil is more viscous than water, for example, and honey is more viscous than mineral oil. Whole blood is 4.5 to 5.5 times as viscous as water. This is due mainly to the RBCs; plasma alone is 2.0 times as viscous as water, mainly because of its protein. Viscosity is important in

[1] *hem, hemato* = blood + *logy* = study of

[2] *erythro* = red + *cyte* = cell

[3] *leuko* = white + *cyte* = cell

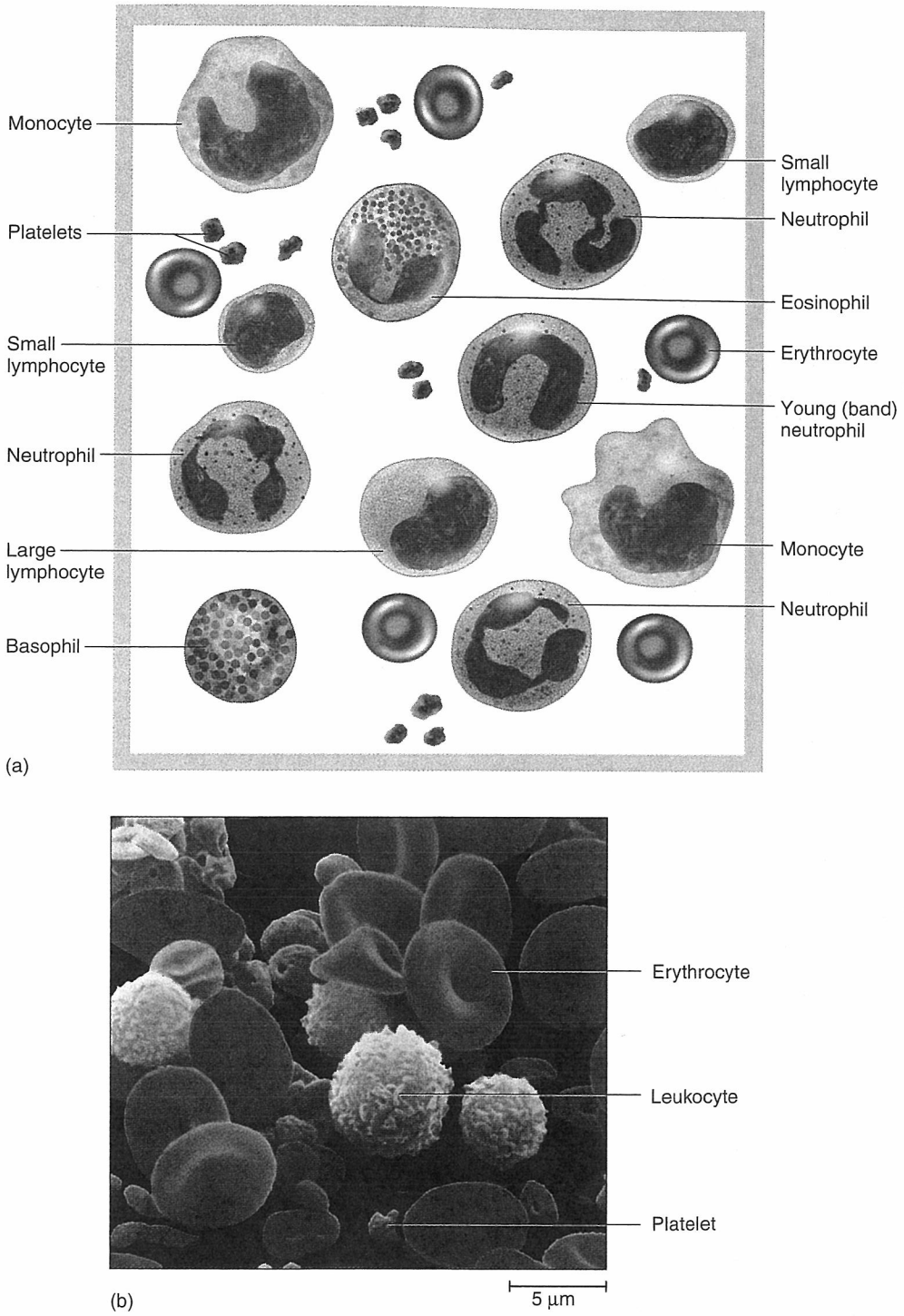


Figure 18.1 The Formed Elements of Blood. (*a*) The structure of red blood cells, white blood cells, and platelets. (*b*) Blood cells and platelets (colorized SEM).
What do erythrocytes and platelets lack that the other formed elements have?

circulatory function because it partially governs the flow of blood through the vessels. An RBC or protein deficiency reduces viscosity and causes blood to flow too easily, whereas an excess causes blood to flow too sluggishly. Either of these conditions puts a strain on the heart that may lead to serious cardiovascular problems if not corrected.

The **osmolarity** of blood (total molarity of its dissolved particles) is another important factor in cardiovascular function. In order to nourish surrounding cells and

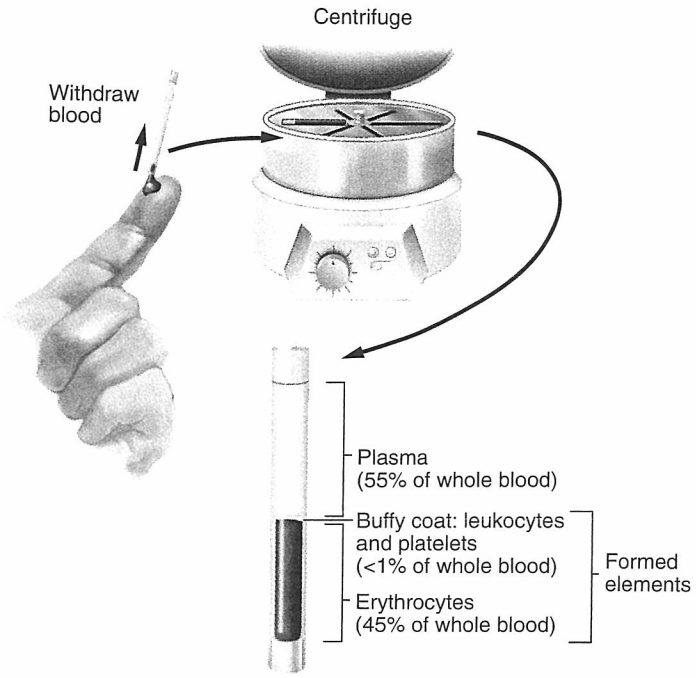


Figure 18.2 The Hematocrit. A small sample of blood is taken in a glass tube and spun in a centrifuge to separate the cells from the plasma. The percent volume of red cells (hematocrit) is then measured. In this example, the hematocrit is 45%.

remove their wastes, substances must pass between the bloodstream and tissue fluid through the capillary walls. This transfer of fluids depends on a balance between the filtration of fluid from the capillary and its reabsorption by osmosis (see fig. 3.15, p. 108). The rate of reabsorption is governed by the relative osmolarity of the blood versus the tissue fluid. If the osmolarity of the blood is too high, the bloodstream absorbs too much fluid, which results in high blood pressure and a potentially dangerous strain on the heart and arteries. If its osmolarity drops too low, too much fluid remains in the tissues. They become edematous (swollen) and the blood pressure may drop to dangerously low levels because of the amount of fluid lost from the bloodstream.

It is therefore important that the blood maintain an optimal osmolarity. The osmolarity of the blood is a product mainly of its sodium ions, protein, and erythrocytes. The contribution of protein to blood osmotic pressure—called the **colloid osmotic pressure (COP)**—is especially important, as we see from the effects of extremely low-protein diets (see insight 18.1).

Before You Go On

Answer the following questions to test your understanding of the preceding section:

1. From your body weight in kilograms, predict how many kilograms and how many liters of blood you have.

Table 18.2 General Properties of Blood*

Mean Fraction of Body Weight	8%
Volume in Adult Body	Female: 4–5 L; male: 5–6 L
Volume/Body Weight	80–85 mL/kg
Mean Temperature	38°C (100.4°F)
pH	7.35–7.45
Viscosity (relative to water)	Whole blood: 4.5–5.5; plasma: 2.0
Osmolarity	280–296 mOsm/L
Mean Salinity (mainly NaCl)	0.9%
Hematocrit (packed cell volume)	Female: 37%–48% male: 45%–52%
Hemoglobin	Female: 12–16 g/dL male: 13–18 g/dL
Mean RBC Count	Female: 4.2–5.4 million/μL male: 4.6–6.2 million/μL
Platelet Count	130,000–360,000/μL
Total WBC Count	5,000–10,000/μL

*Values vary slightly depending on the testing methods used.

2. What are the two principal components of the blood?
3. What percentage of the blood is composed of erythrocytes? What is the term for this percentage?
4. Why is blood viscosity important? What are the main factors that contribute to blood viscosity?
5. Why is blood osmolarity important? What are the main factors that contribute to blood osmolarity?

Insight 18.1 Clinical Application

Starvation and Plasma Protein Deficiency

Several conditions can lead to hypoproteinemia, a deficiency of plasma protein: extreme starvation or dietary protein deficiency, liver diseases that interfere with protein synthesis, kidney diseases that result in protein loss through the urine, and severe burns that result in protein loss through the body surface. As the protein content of the blood plasma drops, so does its osmolarity. The bloodstream loses more fluid to the tissues than it reabsorbs by osmosis. Thus, the tissues become edematous and a pool of fluid may accumulate in the abdominal cavity—a condition called *ascites* (ah-SY-teez).

Children who suffer severe dietary protein deficiencies often exhibit a condition called *kwashiorkor* (KWASH-ee-OR-cor) (fig. 18.3). The arms and legs are emaciated for lack of muscle, the skin is shiny and tight with edema, and the abdomen is swollen by ascites. *Kwashiorkor* is an African word for a "deposed" or "displaced" child who is no longer breast-fed. Symptoms appear when a child is weaned and placed on a diet consisting mainly of rice or other cereals. Children with kwashiorkor often die of diarrhea and dehydration.

Figure 18.3 A Child with Kwashiorkor. Note the thin limbs and fluid-distended abdomen.

Plasma

Objectives

When you have completed this section, you should be able to

- distinguish between plasma and serum;
- list the proteins of blood plasma and state their functions;
- name the nonprotein nitrogenous compounds of blood plasma and explain their significance; and
- list the major nutrients, gases, and electrolytes found in plasma.

Blood plasma is a complex mixture of proteins, enzymes, nutrients, wastes, hormones, and gases (table 18.3). If we allow blood to clot and then remove the solids, we are left with a fluid called the blood **serum,** which is essentially identical to plasma except for the absence of clotting proteins.

Proteins

Protein is the most abundant plasma solute by weight, totaling 6 to 9 g/dL. Plasma proteins play a variety of roles including clotting, defense, and transport. There are three major categories of proteins, the albumins, globulins, and fibrinogen (table 18.4). Many other plasma proteins are indispensable to survival, but they account for less than 1% of the total.

Albumins are the smallest and most abundant plasma proteins. Because of their major contributions to viscosity and osmolarity, pathological changes in albumin concentration strongly influence blood pressure, flow, and fluid balance. **Globulins** are divided into three subclasses; from smallest to largest in molecular weight, they are the alpha (α), beta (β), and gamma (γ) globulins. **Fibrinogen** is a soluble precursor of *fibrin,* a sticky protein that forms the

Table 18.3 Composition of Blood Plasma*

Water	92% by weight
Proteins	Total 6–9 g/dL
Albumins	60% of total protein, 3.2–5.5 g/dL
Globulins	36% of total protein, 2.3–3.5 g/dL
Fibrinogen	4% of total protein, 0.2–0.3 g/dL
Nutrients	
Glucose (dextrose)	70–110 mg/dL
Amino acids	33–51 mg/dL
Lactic acid	6–16 mg/dL
Total lipid	450–850 mg/dL
Cholesterol	120–220 mg/dL
Fatty acids	190–420 mg/dL
High-density lipoprotein (HDL)	30–80 mg/dL
Low-density lipoprotein (LDL)	62–185 mg/dL
Neutral fats (triglycerides)	40–150 mg/dL
Phospholipids	6–12 mg/dL
Iron	50–150 μg/dL
Trace elements	Traces
Vitamins	Traces
Electrolytes	
Sodium (Na^+)	135–145 mEq/L
Calcium (Ca^{2+})	9.2–10.4 mEq/L
Potassium (K^+)	3.5–5.0 mEq/L
Magnesium (Mg^{2+})	1.3–2.1 mEq/L
Chloride (Cl^-)	100–106 mEq/L
Bicarbonate (HCO_3^-)	23.1–26.7 mEq/L
Phosphate (HPO_4^{2-})	1.4–2.7 mEq/L
Sulfate (SO_4^{2-})	0.6–1.2 mEq/L
Nitrogenous Wastes	
Urea	8–25 mg/dL
Uric acid	1.5–8.0 mg/dL
Creatinine	0.6–1.5 mg/dL
Creatine	0.2–0.8 mg/dL
Ammonia	0.02–0.09 mg/dL
Bilirubin	0–1.0 mg/dL
Other Components	
Respiratory gases (O_2, CO_2, N_2)	—
Enzymes of diagnostic value	—
Hormones	—

*This table is limited to substances of greatest relevance to this and later chapters. Concentrations refer to plasma only, not to whole blood.

Table 18.4 Major Proteins of the Blood Plasma

Proteins	Functions
Albumins (60%)*	Responsible for colloid osmotic pressure; major contributor to blood viscosity; transport lipids, hormones, calcium, and other solutes; buffer blood pH
Globulins (36%)*	
Alpha (α) Globulins	
Haptoglobulin	Transports hemoglobin released by dead erythrocytes
Ceruloplasmin	Transports copper
Prothrombin	Promotes blood clotting
Others	Transport lipids, fat-soluble vitamins, and hormones
Beta (β) Globulins	
Transferrin	Transports iron
Complement proteins	Aid in destruction of toxins and microorganisms
Others	Transport lipids
Gamma (γ) Globulins	Antibodies; combat pathogens
Fibrinogen (4%)*	Becomes fibrin, the major component of blood clots

*Mean percentage of the total plasma protein by weight.

framework of a blood clot. Some other plasma proteins are enzymes involved in the clotting process.

The liver produces as much as 4 g of plasma protein per hour, contributing all of the major proteins except γ globulins. The γ globulins, also called antibodies, come from *plasma cells*—connective tissue cells that are descended from white blood cells called *B lymphocytes.*

Think About It

What would be the benefit of giving intravenous albumin to a patient who has experienced fluid loss and low blood volume? Relate your answer to the principle of osmosis.

Nonprotein Nitrogenous Substances

Blood plasma contains several important nitrogenous compounds in addition to protein—notably amino acids and nitrogenous wastes. The amino acids come from the digestion of dietary protein or the catabolism of tissue proteins. **Nitrogenous wastes** are toxic end products of catabolism (see table 18.3). The most abundant is *urea,* a product of amino acid catabolism. Nitrogenous wastes are normally cleared from the blood and excreted by the kidneys at a rate that balances their rate of production.

Nutrients

Nutrients absorbed by the digestive tract are transported in the blood plasma. They include glucose, amino acids, fats, cholesterol, phospholipids, vitamins, and minerals.

Gases

Plasma transports some of the oxygen and carbon dioxide carried by the blood. It also contains a substantial amount of dissolved nitrogen, which normally has no physiological role in the body but becomes important under circumstances such as diving and aviation.

Electrolytes

Electrolytes of the blood plasma are listed in table 18.3. Sodium ions constitute about 90% of the plasma cations and account for more of the blood's osmolarity than any other solute. Sodium therefore has a major influence on blood volume and pressure; people with high blood pressure are thus advised to limit their sodium intake. Electrolyte concentrations are carefully regulated by the body and have rather stable concentrations in the plasma.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

6. List the three major classes of plasma proteins. Which one is missing from blood serum?
7. What are the functions of blood albumin?
8. List some organic and inorganic components of plasma other than protein.

Blood Cell Production

Objectives

When you have completed this section, you should be able to

- explain where blood is produced in fetuses, children, and adults;
- describe the stages of blood cell production and state the factors that influence its rate; and
- explain how uncommitted stem cells become committed to forming specific types of blood cells.

A knowledge of **hemopoiesis**[4] (HE-mo-poy-EE-sis), production of the formed elements of blood, provides a foundation for understanding leukemia, anemia, and other blood disorders. The tissues that produce blood are called *hemopoietic tissues.* The earliest of these to develop is the *yolk sac,* a membrane associated with all vertebrate embryos. In most vertebrates, it encloses the yolk of the egg and functions in both hemopoiesis and the transfer of yolk nutrients to the embryo. Even animals that don't lay eggs, however, have a yolk sac that retains its hemopoietic function. (It is also the source of cells that later produce eggs or sperm.) Cell clusters called *blood islands* form in the yolk sac by the third week of human development. They produce primitive *stem cells* that colonize the fetal bone marrow, liver, spleen, and thymus, where they subsequently produce blood cells.

The liver stops producing blood cells around the time of birth. The spleen stops producing RBCs soon after birth, but it continues to produce lymphocytes for life. From infancy onward, all formed elements are produced by **myeloid**[5] **hemopoiesis** in the red bone marrow and lymphocytes are additionally produced by **lymphoid hemopoiesis** in widely distributed lymphoid tissues and organs. These sites include the thymus, tonsils, lymph nodes, spleen, and patches of lymphoid tissue in the intestines and elsewhere.

The stages of myeloid hemopoiesis are shown in figure 18.4. The process begins with stem cells called **hemocytoblasts,**[6] which multiply continually to maintain their numbers and which are *multipotent*—capable of differentiating into multiple cell lines that give rise to all of the formed elements. Differentiation begins when they develop surface receptors for specific stimulatory chemicals—*erythropoietin, thrombopoietin,* and *colony-stimulating factors (CSFs).* At this point, they can no longer produce more hemocytoblasts; they are called *committed cells* because each is destined to continue down one specific developmental pathway. We'll now examine the three principal pathways—*erythropoiesis, leukopoiesis,* and *thrombopoiesis.*

Erythrocyte Production

Erythrocyte production is called **erythropoiesis** (eh-RITH-ro-poy-EE-sis). It normally generates about 2.5 million RBCs per second (20 mL/day). The sequence of cell transformations leading to an erythrocyte is hemocytoblast → proerythroblast → erythroblast → normoblast → reticulocyte → erythrocyte. The *proerythroblast* is the first committed cell, having receptors for the hormone **erythropoietin (EPO).** Once EPO receptors are in place, the cell is committed exclusively to producing RBCs. EPO is secreted by the kidneys and liver and stimulates proerythroblasts to differentiate into erythroblasts. Erythroblasts multiply and synthesize *hemoglobin* (the red oxygen-transport protein), then discard their nucleus, which shrinks and is lost from the cell. With the nucleus gone, the cell is called a *reticulocyte*—named for a fine network of endoplasmic reticulum (ER) that persists for another day or two. The overall transformation from hemocytoblast to reticulocytes takes 3 to 5 days and involves four major developments—a reduction in cell size, an increase in cell number, the synthesis of hemoglobin, and the loss of the nucleus.

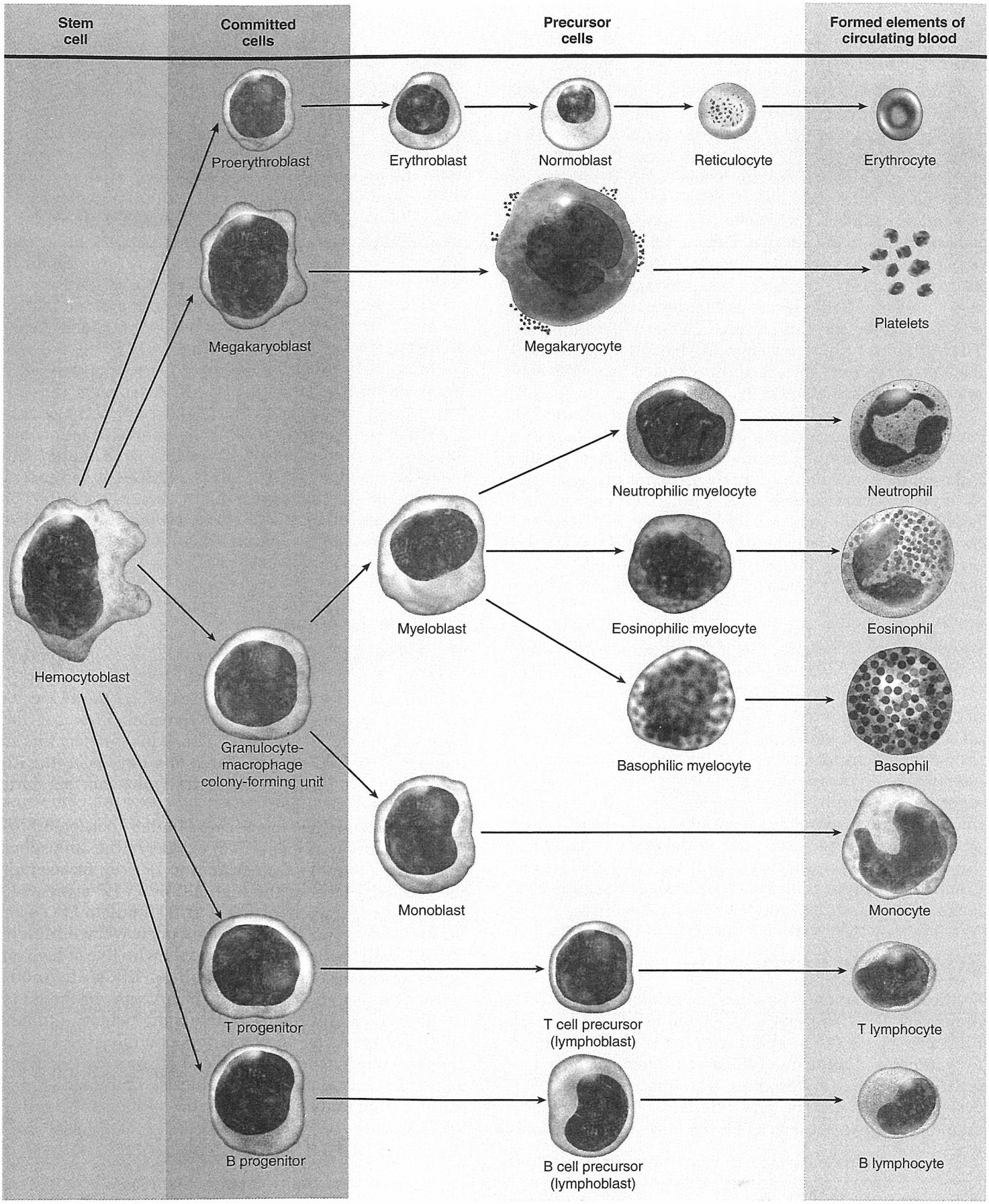
Reticulocytes leave the bone marrow and enter the bloodstream. When the last of the ER disappears, the cell is a mature erythrocyte. About 0.5% to 1.5% of the circulating RBCs are reticulocytes, but this percentage increases under some circumstances. Blood loss, for example, stimulates accelerated erythropoiesis and leads to an increasing number of reticulocytes in circulation—as if the bone marrow were in such a hurry to replenish the lost RBCs that it lets many developing RBCs into circulation a little early.

Erythrocyte Homeostasis

The RBC count is maintained in a classic negative feedback manner (fig. 18.5). If the RBC count should drop (for example, because of hemorrhaging), then the blood will carry less oxygen—a state of **hypoxemia**[7] (oxygen deficiency in the blood) will exist. The kidneys detect this and increase their EPO output. Three or 4 days later, the RBC count begins to rise and reverses the hypoxemia that started the process.

Hypoxemia has many causes other than blood loss. Another cause is a low level of oxygen in the atmosphere. If you were to move from Miami to Denver, for example, the lower O_2 level at the high altitude of Denver would produce temporary hypoxemia and stimulate EPO secretion and erythropoiesis. The blood of an average adult has about 5 million RBCs/μL, but people who live at high altitudes may have counts of 7 to 8 million RBCs/μL. Another cause of hypoxemia is an abrupt increase in the body's oxygen consumption. If a lethargic person suddenly takes up tennis or aerobics, for example, the muscles consume oxygen more rapidly and create a state of hypoxemia that stimulates erythropoiesis. Endurance-trained athletes commonly have RBC counts as high as 6.5 million RBCs/μL.

[4] *hemo* = blood + *poiesis* = formation of
[5] *myel* = bone marrow
[6] *hemo* = blood + *cyto* = cell + *blast* = precursor
[7] *hyp* = below normal + *ox* = oxygen + *emia* = blood condition



igure 18.4 Hemopoiesis. Stages in the development of all the formed elements of blood.

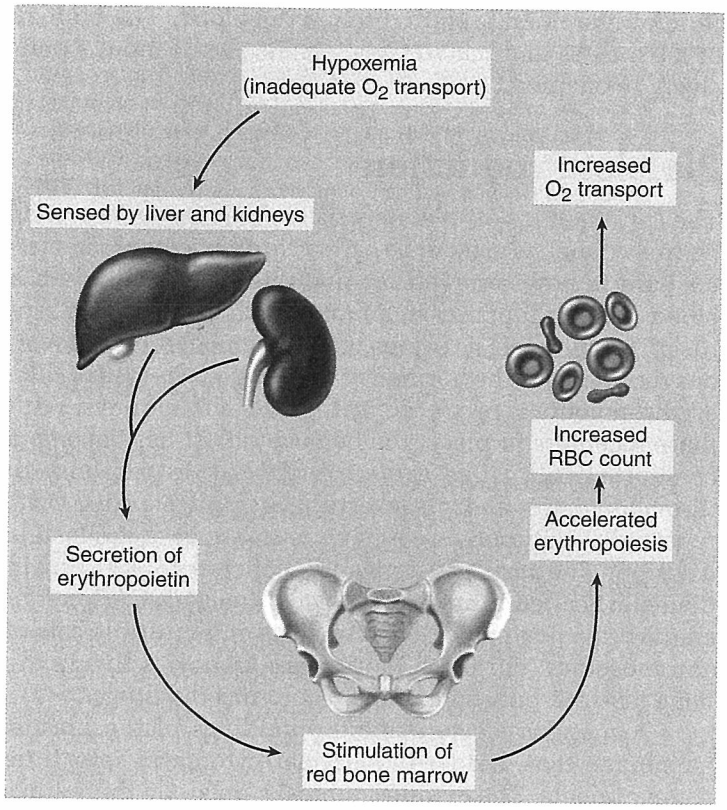


Figure 18.5 The Correction of Hypoxemia Through a Negative Feedback Loop.

Not all hypoxemia can be corrected by increasing erythropoiesis. In emphysema, for example, there is less lung tissue available to oxygenate the blood. Raising the RBC count cannot correct this, but the kidneys and bone marrow have no way of knowing this. The RBC count continues to rise in a futile attempt to restore homeostasis, resulting in a dangerous excess called *polycythemia,* discussed shortly.

Iron Metabolism

Iron is a critical part of the hemoglobin molecule and therefore one of the key nutritional requirements for erythropoiesis. Men lose about 0.9 mg of iron per day through the urine, feces, and bleeding, and women of reproductive age lose an average of 1.7 mg/day because of the added factor of menstruation. Since we absorb only a fraction of the iron in our food, we must consume 5 to 20 mg/day to replace our losses. Pregnant women need 20 to 48 mg/day, especially in the last 3 months, to meet not only their own need but also that of the fetus.

Dietary iron exists in two forms: ferric (Fe^{3+}) and ferrous (Fe^{2+}) ions. Stomach acid converts most Fe^{3+} to Fe^{2+}, the only form that can be absorbed by the small intestine (fig. 18.6). A protein called **gastroferritin,** produced by the stomach, then binds Fe^{2+} and transports it to the small intestine. Here, it is absorbed into the blood, binds to a plasma protein called **transferrin,** and travels to the bone marrow, liver, and other tissues. Bone marrow uses Fe^{2+} for

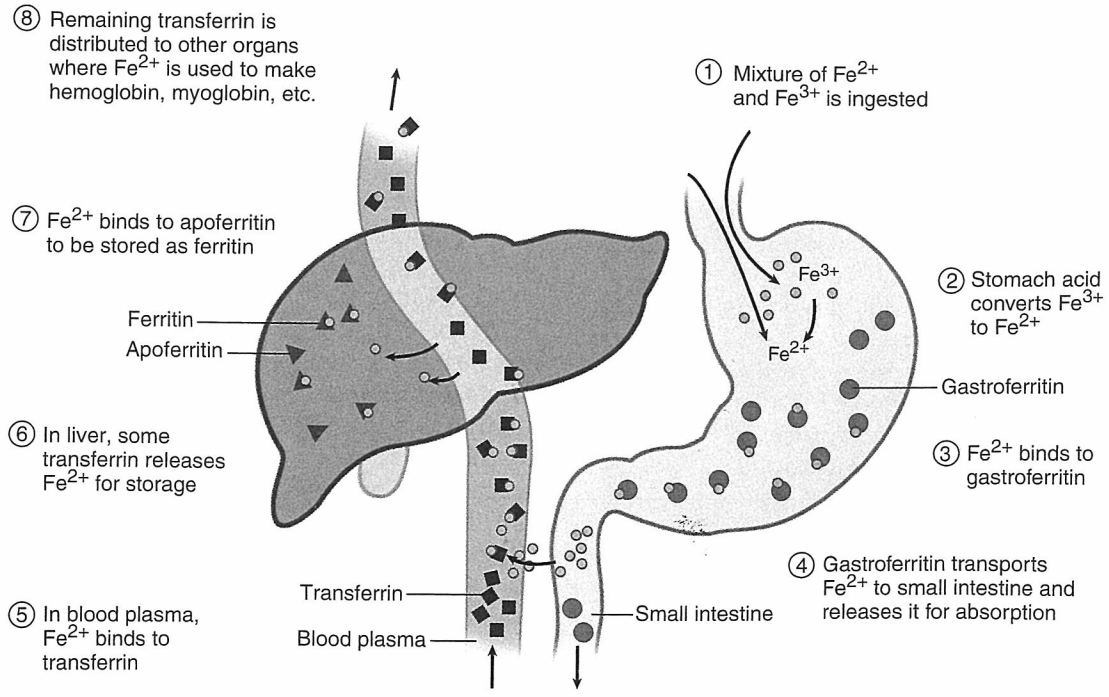


Figure 18.6 The Pathway of Iron Absorption, Transport, and Storage.

hemoglobin synthesis; muscle uses it to make the oxygen-storage protein myoglobin; and nearly all cells use iron to make electron-transport molecules called cytochromes in their mitochondria. The liver binds surplus iron to a protein called **apoferritin,** forming an iron-storage complex called **ferritin.** It releases Fe^{2+} into circulation when needed.

Some other nutritional requirements for erythropoiesis are vitamin B_{12} and folic acid, required for the rapid cell division and DNA synthesis that occurs in erythropoiesis, and vitamin C and copper, which are cofactors for some of the enzymes that synthesize hemoglobin. Copper is transported in the blood by an α globulin called *ceruloplasmin.*[8]

Leukocyte Production

Leukopoiesis (LOO-co-poy-EE-sis) is the production of white blood cells (see fig. 18.4). It begins when some hemocytoblasts differentiate into three types of committed cells:

1. *B progenitors,* destined to become B lymphocytes;
2. *T progenitors,* which become T lymphocytes; and
3. *granulocyte-macrophage colony-forming units,* which become granulocytes and monocytes.

These committed cells have receptors for colony-stimulating factors (CSFs). Mature lymphocytes and macrophages secrete several types of CSFs in response to infections and other immune challenges. Each CSF stimulates a different WBC type to develop in response to specific needs. Thus, a bacterial infection may trigger the production of neutrophils whereas an allergy triggers the production of eosinophils, each process working through its own CSF.

The red bone marrow stores granulocytes and monocytes until they are needed and contains 10 to 20 times more of these cells than the circulating blood does. Lymphocytes begin developing in the bone marrow but do not stay there. Some types mature there and others migrate to the thymus to complete their development. Mature lymphocytes from both locations then colonize the spleen, lymph nodes, and other lymphoid organs and tissues.

Circulating leukocytes do not stay in the blood for very long. Granulocytes circulate for 4 to 8 hours and then migrate into the tissues, where they live another 4 or 5 days. Monocytes travel in the blood for 10 to 20 hours, then migrate into the tissues and transform into a variety of **macrophages** (MAC-ro-fay-jes). Macrophages can live as long as a few years.

Lymphocytes, responsible for long-term immunity, survive from a few weeks to decades; they leave the bloodstream for the tissues and eventually enter the lymphatic system, which empties them back into the bloodstream. Thus, they are continually recycled from blood to tissue fluid to lymph and finally back to the blood. The biology of leukocytes and macrophages is discussed more extensively in chapter 21.

[3] *cerulo* = blue-green, the color of oxidized copper + *plasm* = blood plasma

Platelet Production

The production of platelets is called **thrombopoiesis** because platelets used to be called *thrombocytes.*[9] The latter term is now reserved for nucleated true cells with a blood-clotting function in animals such as birds and reptiles. Thrombopoiesis begins when a hemocytoblast develops receptors for the hormone *thrombopoietin,* which, like erythropoietin, is produced by the liver and kidneys. With these receptors in place, the hemocytoblast has become a committed cell called a *megakaryoblast.* In response to thrombopoietin, the megakaryoblast replicates its DNA repeatedly without undergoing nuclear or cytoplasmic division. The result is a gigantic cell (up to 100 μm in diameter) called a **megakaryocyte**[10] (meg-ah-CAR-ee-oh-site), with a huge multilobed nucleus and multiple sets of chromosomes (fig. 18.7). Most megakaryocytes live in the bone marrow, but some of them colonize the lungs.

A megakaryocyte exhibits infoldings of the plasma membrane that divide its marginal cytoplasm into little compartments. The cytoplasm breaks up along these lines of weakness into tiny fragments that enter the bloodstream. Some of these are functional platelets, while others are larger particles that break up into platelets as they pass through the lungs. About 25% to 40% of the platelets are stored in the spleen and released as needed. The remainder circulate freely in the blood and live for about 10 days.

[9] *thrombo* = clotting + *cyte* = cell
[10] *mega* = giant + *karyo* = nucleus + *cyte* = cell

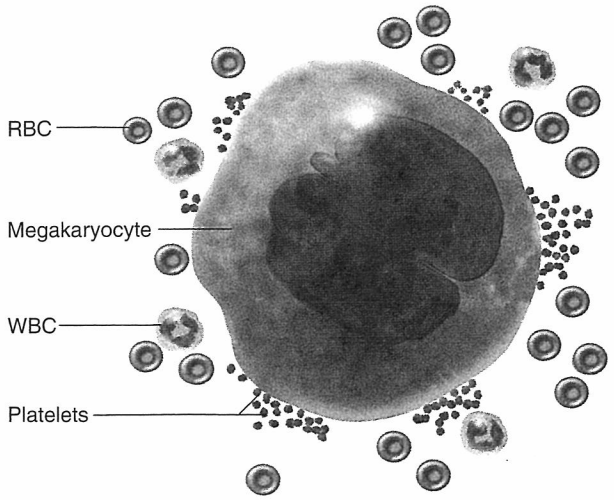


Figure 18.7 A Megakaryocyte Producing Platelets. Several red and white blood cells are shown for size comparison.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

9. List the fetal tissues and organs that produce blood.
10. How do the sites of hemopoiesis differ between children and adults?
11. Distinguish between lymphoid and myeloid hemopoiesis.
12. How is a hemocytoblast different from a committed hemopoietic cell?

Erythrocytes

Objectives

When you have completed this section, you should be able to

- describe the structure of erythrocytes (red blood cells);
- describe the structure and function of hemoglobin;
- describe how the erythrocytes and hemoglobin content of the blood are quantified;
- explain why men and women differ in their erythrocyte count and hemoglobin level;
- describe the life cycle of erythrocytes; and
- describe the types, causes, and effects of anemia and polycythemia.

Form and Function

Erythrocytes have two principal functions: (1) to pick up oxygen from the lungs and deliver it to tissues elsewhere and (2) to pick up carbon dioxide from other tissues and unload it in the lungs. An erythrocyte is a disc-shaped cell with a thick rim and a thin sunken center where the nucleus used to be. It is about 7.5 μm in diameter and 2.0 μm thick at the rim (fig. 18.8).

The plasma membrane of a mature RBC has glycoproteins and glycolipids that determine a person's blood type. On its inner surface are two peripheral proteins, *spectrin* and *actin,* that give the membrane resilience and durability. This is especially important when RBCs pass through small blood capillaries and sinusoids. Many of these passages are narrower than the diameter of an RBC, forcing the RBCs to stretch, bend, and fold as they squeeze through. When they enter larger vessels, they spring back to their discoid shape.

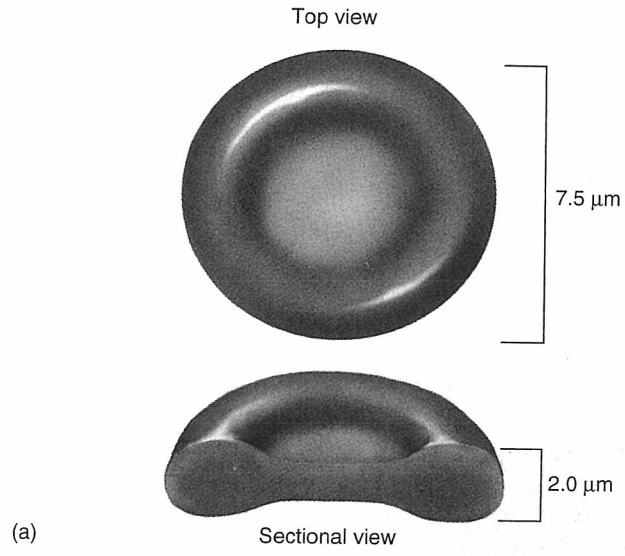
Most cells, including white blood cells, have an abundance of organelles. RBCs, however, lose nearly all of their organelles during maturation and are almost devoid of internal structure (fig. 18.9). Because they lack mitochondria, RBCs are incapable of aerobic respiration. This prevents them from consuming the oxygen they are meant to transport to other tissues. Erythrocytes are the only cells in the body that carry on anaerobic fermentation indefinitely.

The cytoplasm of an RBC consists mainly of a 33% solution of **hemoglobin (Hb),** the red pigment that gives the RBC its color and name. Hemoglobin carries most of the oxygen and some of the carbon dioxide transported by the blood.

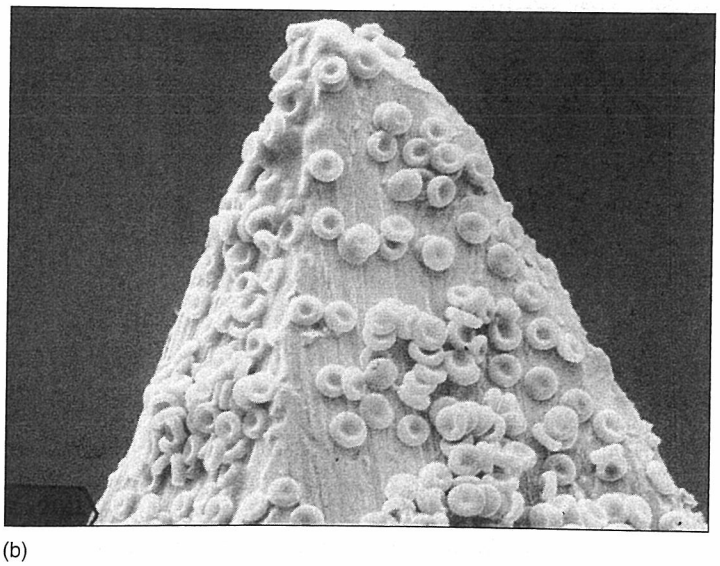
The cytoplasm also contains an enzyme, *carbonic anhydrase (CAH),* that catalyzes the reaction $CO_2 + H_2O \leftrightarrow H_2CO_3$. The role of CAH in gas transport and pH balance is discussed in chapters 22 and 24. The lack of a nucleus makes an RBC unable to repair itself, but it has an overriding advantage: The biconcave shape gives the cell a much greater ratio of surface area to volume, which enables O_2 and CO_2 to diffuse quickly to and from the hemoglobin and CAH.

Hemoglobin

Each erythrocyte contains about 280 million molecules of hemoglobin. Hemoglobin consists of four protein chains



(a)



(b)

Figure 18.8 The Structure of Erythrocytes. (*a*) Dimensions and shape of an erythrocyte. (*b*) Erythrocytes on the tip of a hypodermic needle.

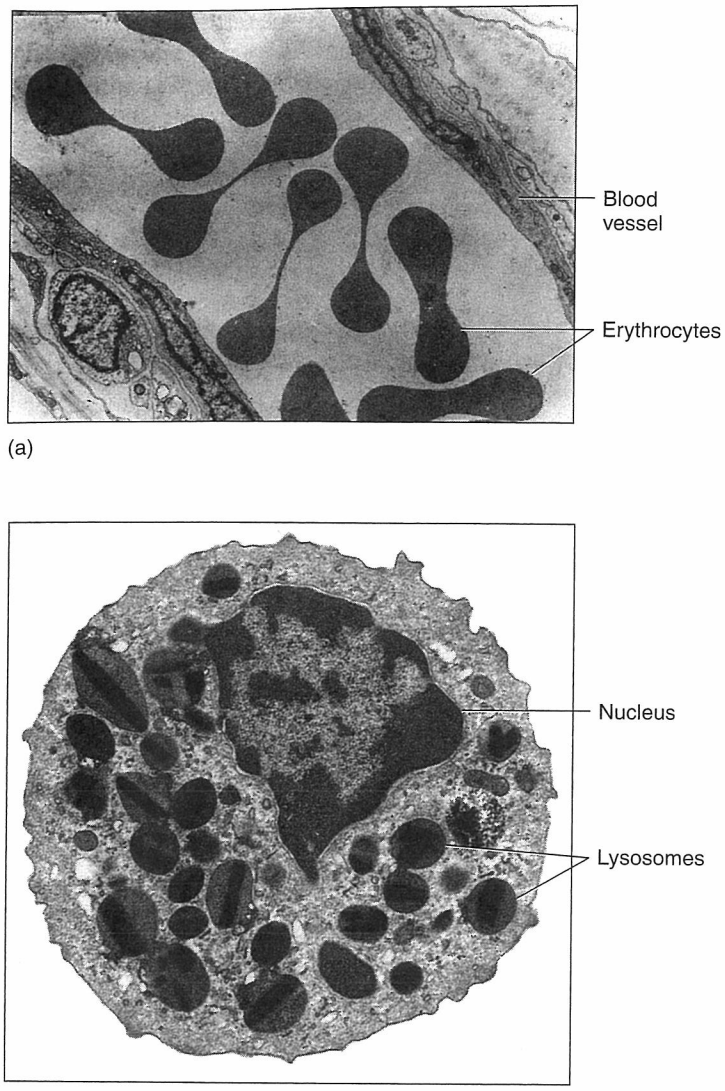


Figure 18.9 Comparison of RBCs and WBCs as Seen with the Transmission Electron Microscope. (*a*) RBCs in a small blood vessel, showing their strongly biconcave shape and lack of organelles. (*b*) An eosinophil, a representative leukocyte, showing a nucleus, many lysosomes, and other organelles.
What is the approximate width of this blood vessel?

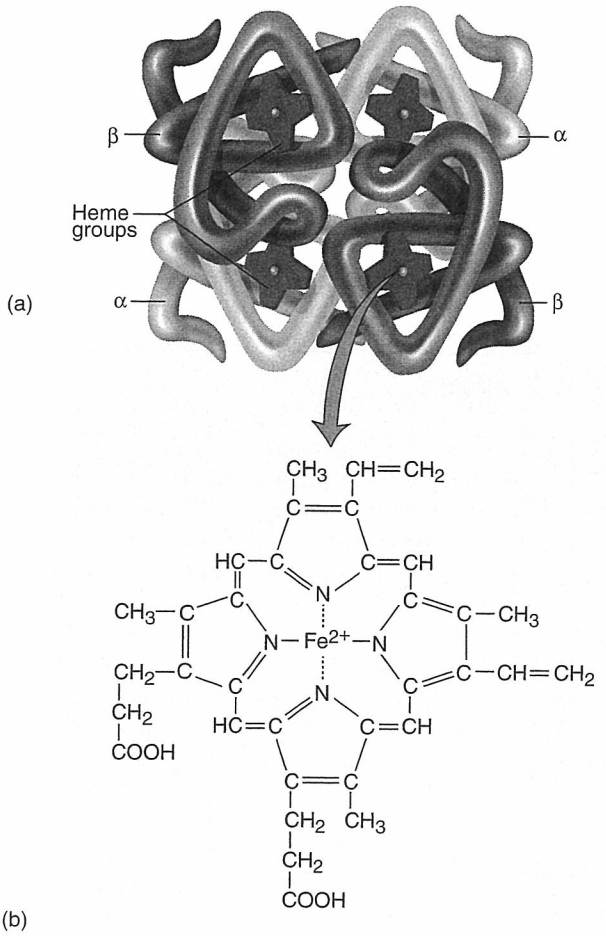


Figure 18.10 The Structure of Adult Hemoglobin (HbA). (*a*) The hemoglobin molecule consists of two α proteins and two β proteins, each conjugated to a nonprotein heme group. (*b*) Structure of the heme group. Oxygen binds to Fe^{2+} at the center of the heme.

called **globins** (fig. 18.10*a*). Two of these, the *alpha* (α) *chains,* are 141 amino acids long, and the other two, the *beta* (β) *chains,* are 146 amino acids long. Each chain is conjugated with a nonprotein moiety called the **heme** group (fig. 18.10*b*), which binds oxygen to a ferrous ion (Fe^{2+}) at its center. Each heme can carry one molecule of O_2; thus, the hemoglobin molecule as a whole can transport up to 4 O_2. About 5% of the CO_2 in the bloodstream is also transported by hemoglobin but is bound to the globin moiety rather than to the heme. Gas transport by hemoglobin is discussed in detail in chapter 22.

Hemoglobin exists in several forms with slight differences in the globin chains. The form we have just described is called *adult hemoglobin (HbA).* About 2.5% of an adult's hemoglobin, however, is of a form called HbA_2, which has two *delta* (δ) *chains* in place of the β chains. The fetus produces a form called *fetal hemoglobin (HbF),* which has two *gamma* (γ) *chains* in place of the β chains. The δ and γ chains are the same length as the β chains but differ in amino acid sequence. HbF binds oxygen more tightly than HbA does; thus it enables the fetus to extract oxygen from the mother's bloodstream.

Insight 18.2 Evolutionary Medicine

The Packaging of Hemoglobin

The gas-transport pigments of earthworms, snails, and many other animals are dissolved in the plasma rather than contained in blood cells.

You might wonder why human hemoglobin must be contained in RBCs. The main reason is osmotic. Remember that the osmolarity of blood depends on the number of particles in solution. A "particle," for this purpose, can be a sodium ion, an albumin molecule, or a whole cell. If all the hemoglobin contained in the RBCs were free in the plasma, it would drastically increase blood osmolarity, since each RBC contains about 280 million molecules of hemoglobin. The circulatory system would become enormously congested with fluid, and circulation would be severely impaired. The blood simply could not contain that much free hemoglobin and support life. On the other hand, if it contained a safe level of free hemoglobin, it could not transport enough oxygen to support the high metabolic demand of the human body. By having our hemoglobin packaged in RBCs, we are able to have much more of it and hence to have more efficient gas transport and more active metabolism.

Quantities of Erythrocytes and Hemoglobin

The RBC count and hemoglobin concentration are important clinical data because they determine the amount of oxygen the blood can carry. Three of the most common measurements are hematocrit, hemoglobin concentration, and RBC count. The **hematocrit**[11] **(packed cell volume, PCV)** is the percentage of whole blood volume composed of RBCs (see fig. 18.2). In men, it normally ranges between 42% and 52%; in women, between 37% and 48%. The **hemoglobin concentration** of whole blood is normally 13 to 18 g/dL in men and 12 to 16 g/dL in women. The **RBC count** is normally 4.6 to 6.2 million RBCs/μL in men and 4.2 to 5.4 million/μL in women. This is often expressed as cells per cubic millimeter (mm^3); 1 μL = 1 mm^3.

Notice that these values tend to be lower in women than in men. There are three physiological reasons for this: (1) androgens stimulate RBC production, and men have higher androgen levels than women; (2) women of reproductive age have periodic menstrual losses; and (3) the hematocrit is inversely proportional to percent body fat, which is higher in women than in men. In men, the blood also clots faster and the skin has fewer blood vessels than in women. Such differences are not limited to humans. From the evolutionary standpoint, the adaptive value of these differences may lie in the fact that male animals fight more than females and suffer more injuries. The traits described here may serve to minimize or compensate for their blood loss.

Think About It

Explain why the hemoglobin concentration could appear deceptively high in a patient who is dehydrated.

[11] *hemato* = blood + *crit* = to separate

Erythrocyte Death and Disposal

Circulating erythrocytes live for about 120 days. The life of an RBC is summarized in figure 18.11. As an RBC ages and its membrane proteins (especially spectrin) deteriorate, the membrane grows increasingly fragile. Without a nucleus or ribosomes, an RBC cannot synthesize new spectrin. Many RBCs die in the spleen, which has been called the "erythrocyte graveyard." The spleen has channels as narrow as 3 μm that severely test the ability of old, fragile RBCs to squeeze through the organ. Old cells become trapped, broken up, and destroyed. An enlarged and tender spleen may indicate diseases in which RBCs are rapidly breaking down.

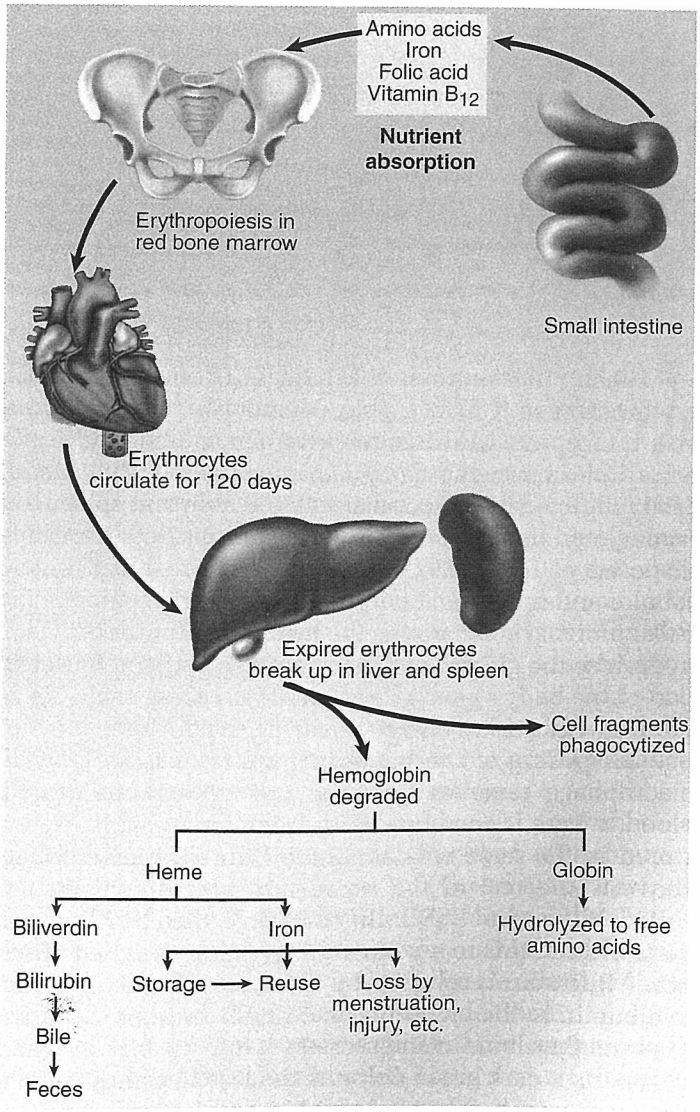


Figure 18.11 The Life and Death of Erythrocytes. Note especially the stages of hemoglobin breakdown and disposal.

Table 18.5 The Fate of Expired Erythrocytes and Hemoglobin

1. RBCs lose elasticity with age
2. RBCs break down while squeezing through blood capillaries and sinusoids
3. Cell fragments are phagocytized by macrophages in the spleen and liver
4. Hemoglobin decomposes into:

   Globin portion—hydrolyzed to amino acids, which can be reused

   Heme portion—further decomposed into:

   Iron

   1. Transported by albumin to bone marrow and liver
   2. Some used in bone marrow to make new hemoglobin
   3. Excess stored in liver as ferritin

   Biliverdin

   1. Converted to bilirubin and bound to albumin
   2. Removed by liver and secreted in bile
   3. Stored and concentrated in gallbladder
   4. Discharged into small intestine
   5. Converted by intestinal bacteria to urobilinogen
   6. Excreted in feces

Table 18.5 outlines the process of disposing of old erythrocytes and hemoglobin. **Hemolysis**[12] (he-MOLL-ih-sis), the rupture of RBCs, releases hemoglobin and leaves empty plasma membranes. The membrane fragments are easily digested by macrophages in the liver and spleen, but hemoglobin disposal is a bit more complicated. It must be disposed of efficiently, however, or it can block kidney tubules and cause renal failure. Macrophages begin the disposal process by separating the heme from the globin. They hydrolyze the globin into free amino acids, which become part of the body's general pool of amino acids available for protein synthesis or energy-releasing catabolism.

Disposing of the heme is another matter. First, the macrophage removes the iron and releases it into the blood, where it combines with transferrin and is used or stored in the same way as dietary iron. The macrophage converts the rest of the heme into a greenish pigment called **biliverdin**[13] (BIL-ih-VUR-din), then further converts most of this to a yellow-green pigment called **bilirubin.**[14] Bilirubin is released by the macrophages and binds to albumin in the blood plasma. The liver removes bilirubin from the albumin and secretes it into the bile, to which it imparts a dark green color as the bile becomes concentrated in the gallbladder. Biliverdin and bilirubin are collectively known as **bile pigments.** The gallbladder discharges the bile into the small intestine, where bacteria convert bilirubin to *urobilinogen,* responsible for the brown color of the feces. Another hemoglobin breakdown pigment, *urochrome,* produces the yellow color of urine. A high level of bilirubin in the blood causes *jaundice,* a yellowish cast in light-colored skin and the whites of eyes. Jaundice may be a sign of rapid hemolysis or a liver disease or bile duct obstruction that interferes with bilirubin disposal.

[12] *hemo* = blood + *lysis* = splitting, breakdown
[13] *bili* = bile + *verd* = green + *in* = substance
[14] *bili* = bile + *rub* = red + *in* = substance

Erythrocyte Disorders

Any imbalance between the rates of erythropoiesis and RBC destruction may produce an excess or deficiency of red cells. An RBC excess is called *polycythemia*[15] (POL-ee-sy-THEE-me-uh), and a deficiency of either RBCs or hemoglobin is called *anemia.*[16]

Polycythemia

Primary polycythemia (*polycythemia vera*) is due to cancer of the erythropoietic line of the red bone marrow. It can result in an RBC count as high as 11 million RBCs/μL and a hematocrit as high as 80%. Polycythemia from all other causes, called **secondary polycythemia,** is characterized by RBC counts as high as 6 to 8 million RBCs/μL. It can result from dehydration because water is lost from the bloodstream while erythrocytes remain and become abnormally concentrated. More often, it is caused by smoking, air pollution, emphysema, high altitude, strenuous physical conditioning, or other factors that create a state of hypoxemia and stimulate erythropoietin secretion.

The principal dangers of polycythemia are increased blood volume, pressure, and viscosity. Blood volume can double in primary polycythemia and cause the circulatory system to become tremendously engorged. Blood viscosity may rise to three times normal. Circulation is poor, the capillaries are clogged with viscous blood, and the heart is dangerously strained. Chronic (long-term) polycythemia can lead to embolism, stroke, or heart failure. The deadly consequences of emphysema and some other lung diseases are due in part to polycythemia.

Anemia

The causes of **anemia** fall into three categories: (1) inadequate erythropoiesis or hemoglobin synthesis, (2) **hemorrhagic anemia** from bleeding, and (3) **hemolytic anemia** from RBC destruction. Table 18.6 gives specific examples and causes for each category. We give special attention to

[15] *poly* = many + *cyt* = cell + *hem* = blood + *ia* = condition
[16] *an* = without + *em* = blood + *ia* = condition

Table 18.6 Types and Causes of Anemia

Anemia Due to Inadequate Erythropoiesis
Inadequate nutrition
Iron-deficiency anemia
Folic acid, vitamin B_{12}, or vitamin C deficiency
Pernicious anemia (deficiency of intrinsic factor)
Renal failure (reduced erythropoietin secretion)
Old age
Renal atrophy (reduced erythropoietin secretion)
Nutritional deficiencies
Insufficient exercise
Destruction of myeloid tissue (hypoplastic and aplastic anemia)
Radiation exposure
Viral infection
Autoimmune disease
Some drugs and poisons (arsenic, mustard gas, benzene, etc.)
Hemorrhagic Anemia, Due to Excessive Bleeding
Trauma, hemophilia, menstruation, ulcer, ruptured aneurysm, etc.
Hemolytic Anemia, Due to Erythrocyte Destruction
Mushroom toxins, snake and spider venoms
Some drug reactions (such as penicillin allergy)
Malaria (invasion and destruction of RBCs by certain parasites)
Sickle-cell disease and thalassemia (hereditary hemoglobin defects)
Hemolytic disease of the newborn (mother-fetus Rh mismatch)

the deficiencies of erythropoiesis and some forms of hemolytic anemia.

Anemia often results from kidney failure, because RBC production depends on the hormone erythropoietin (EPO), which is produced mainly by the kidneys. Erythropoiesis also declines with age, simply because the kidneys atrophy with age and produce less and less EPO as we get older. Compounding this problem, elderly people tend to get less exercise and to eat less well, and both of these factors reduce erythropoiesis.

Nutritional anemia results from a dietary deficiency of any of the requirements for erythropoiesis discussed earlier. Its most common form is **iron-deficiency anemia. Pernicious anemia** can result from a deficiency of vitamin B_{12}, but this vitamin is so abundant in meat that a B_{12} deficiency is rare except in strict vegetarians. More often, it occurs when glands of the stomach fail to produce a substance called **intrinsic factor** that the small intestine needs to absorb vitamin B_{12}. This becomes more common in old age because of atrophy of the stomach. Pernicious anemia can also be hereditary. It is treatable with vitamin B_{12} injections; oral B_{12} would be useless because the digestive tract cannot absorb it without intrinsic factor.

Hypoplastic[17] *anemia* is caused by a decline in erythropoiesis, whereas the complete failure or destruction of the myeloid tissue produces *aplastic anemia,* a complete cessation of erythropoiesis. Aplastic anemia leads to grotesque tissue necrosis and blackening of the skin. Most victims die within a year. About half of all cases are of unknown or hereditary cause, especially in adolescents and young adults. Other causes are given in table 18.6.

Anemia has three potential consequences:

1. The tissues suffer **hypoxia** (oxygen deprivation). The individual is lethargic and becomes short of breath upon physical exertion. The skin is pallid because of the deficiency of hemoglobin. Severe anemic hypoxia can cause life-threatening necrosis of brain, heart, and kidney tissues.
2. Blood osmolarity is reduced. More fluid is thus transferred from the bloodstream to the intercellular spaces, resulting in edema.
3. Blood viscosity is reduced. Because the blood puts up so little resistance to flow, the heart beats faster than normal and cardiac failure may ensue. Blood pressure also drops because of the reduced volume and viscosity.

Sickle-Cell Disease

Sickle-cell disease and thalassemia (see table 18.10) are hereditary hemoglobin defects that occur mostly among people of African and Mediterranean descent, respectively. About 1.3% of African Americans have **sickle-cell disease.** This disorder is caused by a recessive allele that modifies the structure of hemoglobin. Sickle-cell hemoglobin (HbS) differs from normal HbA only in the sixth amino acid of the β chain, where HbA has glutamic acid and HbS has valine. People who are homozygous for HbS exhibit sickle-cell disease. People who are heterozygous for it—about 8.3% of African Americans—have *sickle-cell trait* but rarely have severe symptoms. However, if two carriers reproduce, their children each have a 25% chance of being homozygous and having the disease.

Without treatment, a child with sickle-cell disease has little chance of living to age 2, but even with the best available treatment, few victims live to the age of 50. HbS does not bind oxygen very well. At low oxygen concentrations, it becomes deoxygenated, polymerizes, and forms a gel that causes the erythrocytes to become elongated and pointed at the ends (fig. 18.12), hence the name of the disease. Sickled erythrocytes are sticky; they **agglutinate**[18] (clump together) and block small blood vessels, causing intense pain in oxygen-starved tissues. Blockage of the

[17] *hypo* = below normal + *plas* = formation + *tic* = pertaining to
[18] *ag* = together + *glutin* = glue

circulation can also lead to kidney or heart failure, stroke, rheumatism, or paralysis. Hemolysis of the fragile cells causes anemia and hypoxemia, which triggers further sickling in a deadly positive feedback loop. Chronic hypoxemia also causes fatigue, weakness, mental deficiency, and deterioration of the heart and other organs. In a futile effort to counteract the hypoxemia, the hemopoietic tissues become so active that bones of the cranium and elsewhere become enlarged and misshapen. The spleen reverts to a hemopoietic role, while also disposing of dead RBCs, and becomes enlarged and fibrous. Sickle-cell disease is a prime example of *pleiotropy*—the occurrence of multiple phenotypic effects from a change in a single gene (see p. 148).

Why does sickle-cell disease exist? In Africa, where it originated, vast numbers of people die of malaria. Malaria is caused by a parasite that invades the RBCs and feeds on hemoglobin. Sickle-cell hemoglobin, HbS, is indigestible to malaria parasites, and people heterozygous for sickle-cell disease are resistant to malaria. The lives saved by this gene outnumber the deaths of homozygous individuals, so the gene persists in the population.

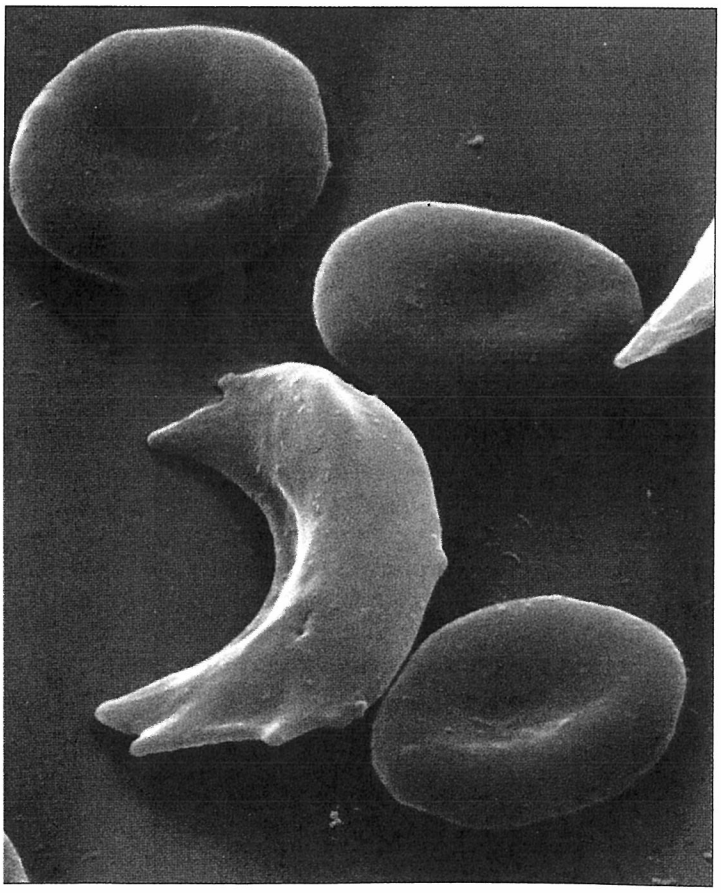


Figure 18.12 Blood of a Person with Sickle-Cell Disease.
Note the deformed, pointed erythrocyte.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

13. Describe the shape, size, and contents of an erythrocyte, and explain how it acquires its unusual shape.
14. What is the function of hemoglobin? What are its protein and nonprotein moieties called?
15. What happens to each of these moieties when old erythrocytes break up?
16. What is the body's primary mechanism for correcting hypoxemia? How does this illustrate homeostasis?
17. What are the three primary causes or categories of anemia? What are its three primary consequences?

Blood Types

Objectives

When you have completed this section, you should be able to

- explain what determines a person's ABO and Rh blood types and how this relates to transfusion compatibility;
- describe the effect of an incompatibility between mother and fetus in Rh blood type; and
- list some blood groups other than ABO and Rh and explain how they may be useful.

Blood types and transfusion compatibility are a matter of interactions between plasma proteins and erythrocytes. Ancient Greek physicians attempted to transfuse blood from one person to another by squeezing it from a pig's bladder through a porcupine quill into the recipient's vein. While some patients benefited from the procedure, it was fatal to others. The reason some people have compatible blood and some do not remained obscure until 1900, when Karl Landsteiner discovered blood types A, B, and O—a discovery that won him a Nobel Prize in 1930; type AB was discovered later. World War II stimulated great improvements in transfusions, blood banking, and blood substitutes (see insight 18.3).

Insight 18.3 Medical History

Charles Drew—Blood Banking Pioneer

Charles Drew (fig. 18.13) was a scientist who lived and died in the arms of bitter irony. After receiving his M.D. from McGill University of Montreal in 1933, Drew became the first black person to pursue the advanced degree of Doctor of Science in Medicine, for which he studied transfusion and blood-banking procedures at Columbia University. He became the director of a new blood bank at Columbia Presbyterian Hospital in 1939 and organized numerous blood banks during World War II.

Drew saved countless lives by convincing physicians to use plasma rather than whole blood for battlefield and other emergency transfusions. Whole blood could be stored for only a week and given only to

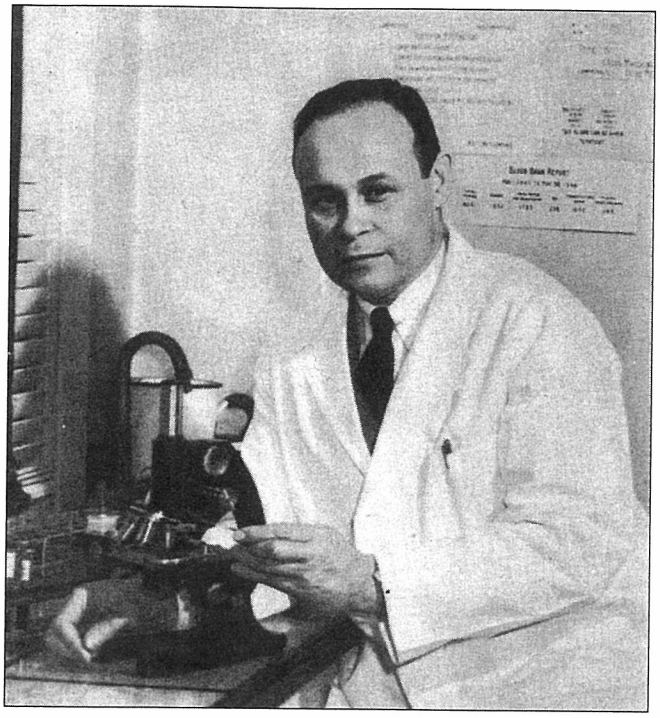


Figure 18.13 Charles Drew (1904–50).

recipients with compatible blood types. Plasma could be stored longer and was less likely to cause transfusion reactions.

When the U.S. War Department issued a directive forbidding the mixing of Caucasian and Negro blood in military blood banks, Drew denounced the order and resigned his position. He became a professor of surgery at Howard University in Washington, D.C., and later chief of staff at Freedmen's Hospital. He was a mentor for numerous young black physicians and campaigned to get them accepted into the medical community. The American Medical Association, however, firmly refused to admit black members, even Drew himself.

Late one night in 1950, Drew and three colleagues set out to volunteer their medical services to an annual free clinic in Tuskegee, Alabama. Drew fell asleep at the wheel and was critically injured in the resulting accident. Doctors at the nearest hospital administered blood and attempted unsuccessfully to revive him. For all the lives he saved through his pioneering work in blood transfusion, Drew himself bled to death at the age of 45.

All cells have an inherited combination of proteins, glycoproteins, and glycolipids on their surfaces. These function as *antigens* that enable our immune system to distinguish our own cells from foreign invaders. Part of the immune response is the production of γ globulins called *antibodies* to combat the invader. In blood typing, the antigens of RBC surfaces are also called *agglutinogens* (ah-glue-TIN-oh-jens) because they are partially responsible for RBC agglutination in mismatched transfusions. The plasma antibodies that react against them are also called *agglutinins* (ah-GLUE-tih-nins).

The ABO Group

Blood types A, B, AB, and O form the **ABO blood group** (table 18.7). Your ABO blood type is determined by the hereditary presence or absence of antigens A and B on your RBCs. The genetic determination of blood types is explained on page 148. The antigens are glycoproteins and glycolipids—membrane proteins and phospholipids with short carbohydrate chains bonded to them. Figure 18.14 shows how these carbohydrates determine the ABO blood types.

Think About It

Suppose you could develop an enzyme that selectively split N-acetylgalactosamine off the glycolipid of type A blood cells (fig. 18.14). What would be the potential benefit of this product to blood banking and transfusion?

The antibodies of the ABO group begin to appear in the plasma 2 to 8 months after birth. They reach their maximum concentrations between 8 and 10 years of age and then slowly decline for the rest of one's life. They are produced mainly in response to the bacteria that inhabit our intestines, but they cross-react with RBC antigens and are therefore best known for their significance in transfusions.

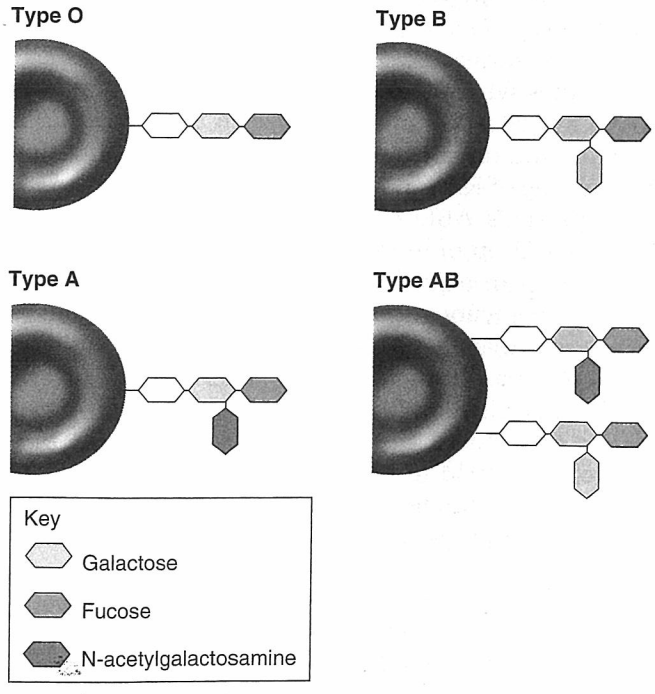


Figure 18.14 Chemical Basis of the ABO Blood Types. The terminal carbohydrates of the antigenic glycolipids are shown. All of them end with galactose and fucose (not to be confused with fructose). In type A, the galactose also has an N-acetylgalactosamine added to it; in type B, it has another galactose; and in type AB, both of these chain types are present.

Table 18.7 The ABO Blood Group

	ABO Blood Type			
	Type O	**Type A**	**Type B**	**Type AB**
Possible Genotypes	*ii*	$I^A I^A, I^A i$	$I^B I^B, I^B i$	$I^A I^B$
RBC Antigen	None	A	B	A,B
Plasma Antibody	Anti-A, anti-B	Anti-B	Anti-A	None
Compatible Donor RBCs	O	O, A	O, B	O, A, B, AB
Incompatible Donor RBCs	A, B, AB	B, AB	A, AB	None
Frequency in U.S. Population				
White	45%	40%	11%	4%
Black	49%	27%	20%	4%
Hispanic	63%	14%	20%	3%
Japanese	31%	38%	22%	9%
Native American	79%	16%	4%	<1%

AB antibodies react against any AB antigen except those on one's own RBCs. The antibody that reacts against antigen A is called α *agglutinin,* or *anti-A;* it is present in the plasma of people with type O or type B blood—that is, anyone who does *not* possess antigen A. The antibody that reacts against antigen B is β *agglutinin,* or *anti-B,* and is present in type O and type A individuals—those who do not possess antigen B. Each antibody molecule has 10 binding sites where it can attach to either an A or B antigen. An antibody can therefore attach to several RBCs at once and bind them together (fig. 18.15). **Agglutination** is the clumping of RBCs bound together by antibodies.

A person's ABO blood type can be determined by placing one drop of blood in a pool of anti-A serum and another drop in a pool of anti-B serum. Blood type AB exhibits conspicuous agglutination in both antisera; type A or B agglutinates only in the corresponding antiserum; and type O does not agglutinate in either one (fig. 18.16).

Type O blood is the most common and AB is the rarest in the United States. Percentages differ from one region of the world to another and among ethnic groups because people tend to marry within their locality and ethnic group and perpetuate statistical variations particular to that group.

In giving transfusions, it is imperative that the donor's RBCs not agglutinate as they enter the recipient's bloodstream. For example, if type B blood were transfused into a type A recipient, the recipient's anti-B antibodies would immediately agglutinate the donor's RBCs (fig. 18.17). A mismatched transfusion causes a **transfusion reaction**—the agglutinated RBCs block small blood vessels, hemolyze, and release their hemoglobin over the next few hours to days. Free hemoglobin can block the kidney tubules and cause death from acute renal failure within a week or so. For this reason, a person with type A (anti-B) blood must never be given a transfusion of type B or AB blood. A person with type B (anti-A) must never receive type A or AB blood. Type O (anti-A and anti-B) individuals cannot safely receive type A, B, or AB blood.

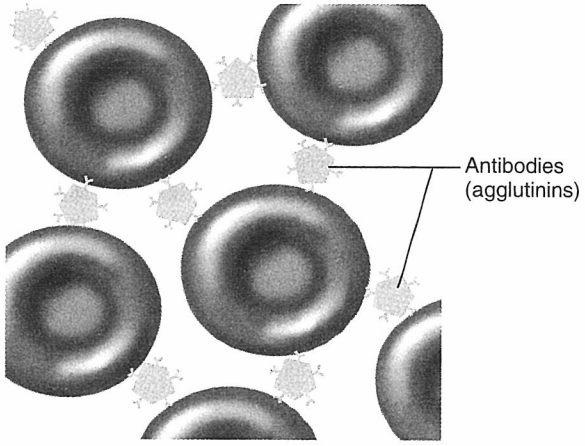


Figure 18.15 Agglutination of RBCs by an Antibody. Anti-A and anti-B have 10 binding sites, located at the 2 tips of each of the 5 Ys, and can therefore bind multiple RBCs to each other.

Type AB is sometimes called the *universal recipient* because this blood type lacks both anti-A and anti-B antibodies; thus, it will not agglutinate donor RBCs of any ABO type. However, this overlooks the fact that the *donor's* plasma can agglutinate the *recipient's* RBCs if it contains anti-A, anti-B, or both. For similar reasons, type O is sometimes called the *universal donor.* The plasma of a type O donor, however, can agglutinate the RBCs of a type A, B, or AB recipient. There are procedures for reduc-

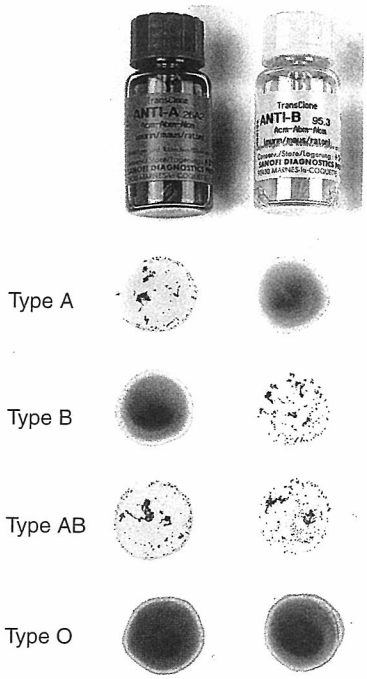


Figure 18.16 ABO Blood Typing. Each row shows the appearance of a drop of blood mixed with anti-A and anti-B antisera. Blood cells become clumped if they possess the antigens for the antiserum *(top row left, second row right, third row both)* but otherwise remain uniformly mixed. Thus type A agglutinates only in anti-A; type B agglutinates only in anti-B; type AB agglutinates in both; and type O agglutinates in neither of them.

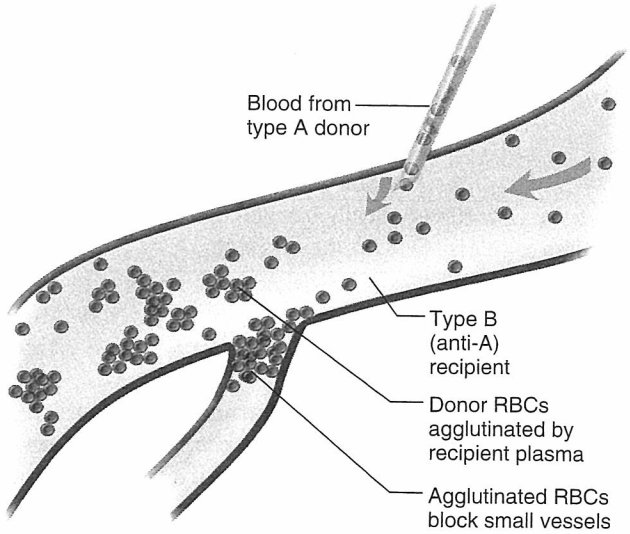


Figure 18.17 Effects of a Mismatched Transfusion. Donor RBCs become agglutinated in the recipient's blood plasma. The agglutinated RBCs lodge in smaller blood vessels downstream from this point and cut off the blood flow to vital tissues.

ing the risk of a transfusion reaction in certain mismatches, however, such as giving packed RBCs with a minimum of plasma.

Contrary to some people's belief, blood type is not changed by transfusion. It is fixed at conception and remains the same for life.

The Rh Group

The **Rh blood group** is named for the rhesus monkey, in which the Rh antigens were discovered in 1940. This group is determined by three genes called C, D, and E, each of which has two alleles: *C, c, D, d, E, e*. Whatever other alleles a person may have, anyone with genotype *DD* or *Dd* has D antigens on his or her RBCs and is classified as *Rh-positive* (Rh^+). In *Rh-negative* (Rh^-) people, the D antigen is lacking. The Rh blood type is tested by using an anti-D reagent. The Rh type is usually combined with the ABO type in a single expression such as O^+ for type O, Rh-positive, or AB^- for type AB, Rh-negative. About 85% of white Americans are Rh^+ and 15% are Rh^-. ABO blood type has no influence on Rh type, or vice versa. If the frequency of type O whites in the United States is 45%, and 85% of these are also Rh^+, then the frequency of O^+ individuals is the product of these separate frequencies: $0.45 \times 0.85 = 0.38$, or 38%. Rh frequencies vary among ethnic groups just as ABO frequencies do. About 99% of Asians are Rh^+, for example.

Think About It

Predict what percentage of Japanese Americans have type B^- blood.

In contrast to the ABO group, anti-D antibodies are not normally present in the blood. They form only in Rh^- individuals who are exposed to Rh^+ blood. If an Rh^- person receives an Rh^+ transfusion, the recipient produces anti-D. Since anti-D does not appear instantaneously, this presents little danger in the first mismatched transfusion. But if that person should later receive another Rh^+ transfusion, his or her anti-D could agglutinate the donor's RBCs.

A related condition sometimes occurs when an Rh^- woman carries an Rh^+ fetus. The first pregnancy is likely to be uneventful because the placenta normally prevents maternal and fetal blood from mixing. However, at the time of birth, or if a miscarriage occurs, placental tearing exposes the mother to Rh^+ fetal blood. She then begins to produce anti-D antibodies (fig. 18.18). If she becomes pregnant again with an Rh^+ fetus, her anti-D antibodies may pass through the placenta and agglutinate the fetal erythrocytes. Agglutinated RBCs hemolyze, and the baby is born with a severe anemia called **hemolytic disease of the newborn (HDN),** or **erythroblastosis fetalis.** Not all HDN is due to Rh incompatibility, however. About 2% of cases

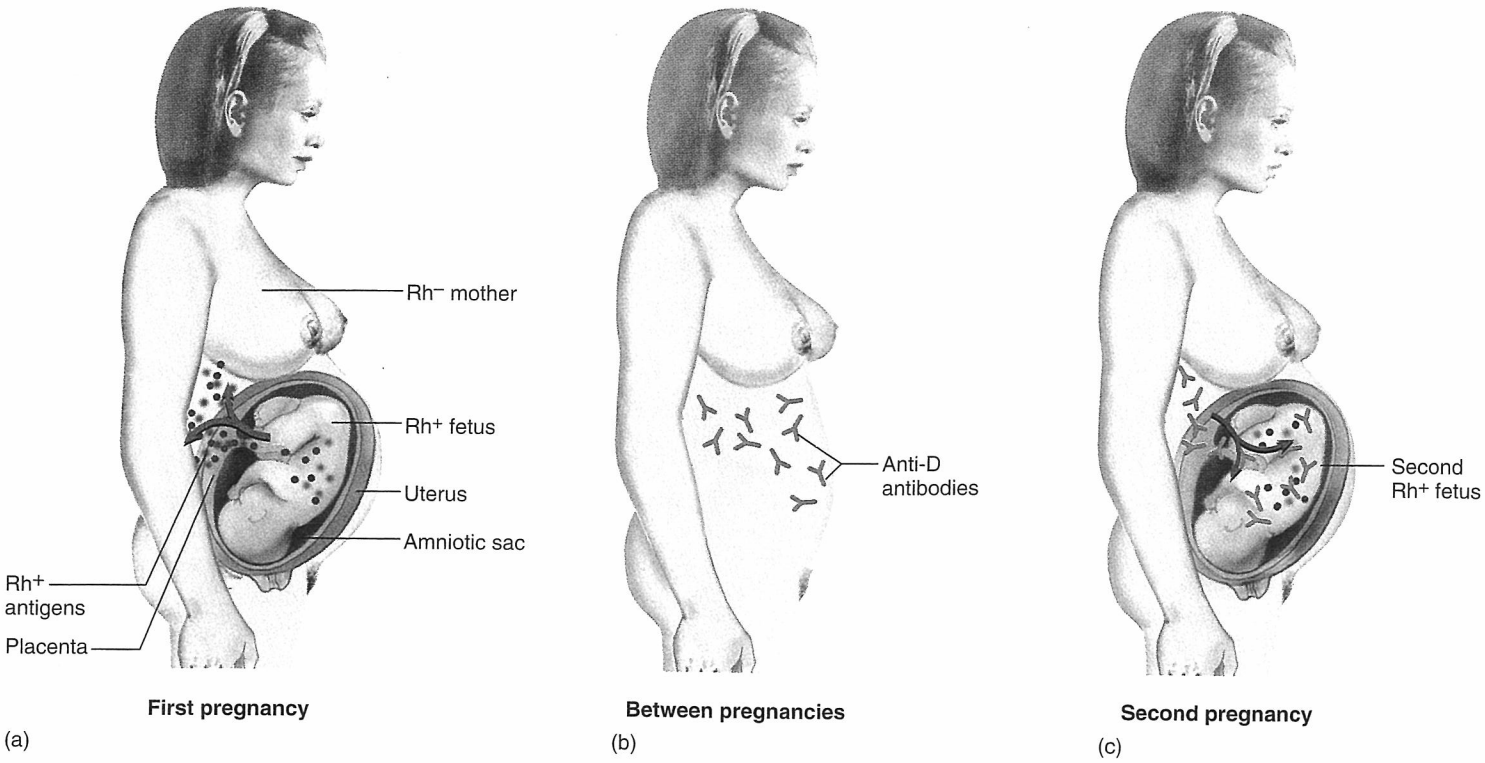


Figure 18.18 Hemolytic Disease of the Newborn (HDN). (*a*) When an Rh^- woman is pregnant with an Rh^+ fetus, she is exposed to D (Rh) antigens, especially during childbirth. (*b*) Following that pregnancy, her immune system produces anti-D antibodies. (*c*) If she later becomes pregnant with another Rh^+ fetus, her anti-D antibodies can cross the placenta and agglutinate the blood of that fetus, causing that child to be born with HDN.

result from incompatibility of ABO and other blood types. About 1 out of 10 cases of ABO incompatibility between mother and fetus results in HDN.

HDN, like so many other disorders, is easier to prevent than to treat. If an Rh^- woman gives birth to (or miscarries) an Rh^+ child, she can be given an *Rh immune globulin* (sold under trade names such as RhoGAM and Gamulin). The immune globulin binds fetal RBC antigens so they cannot stimulate her immune system to produce anti-D. It is now common to give immune globulin at 28 to 32 weeks' gestation and at birth in any pregnancy in which the mother is Rh^- and the father is Rh^+.

If an Rh^- woman has had one or more previous Rh^+ pregnancies, her subsequent Rh^+ children have about a 17% probability of being born with HDN. Infants with HDN are usually severely anemic. As the fetal hemopoietic tissues respond to the need for more RBCs, erythroblasts (immature RBCs) enter the circulation prematurely—hence the name *erythroblastosis fetalis*. Hemolyzed RBCs release hemoglobin, which is converted to bilirubin. High bilirubin levels can cause *kernicterus,* a syndrome of toxic brain damage that may kill the infant or leave it with motor, sensory, and mental deficiencies. HDN can be treated with *phototherapy*—exposing the infant to ultraviolet light, which degrades bilirubin as blood passes through the capillaries of the skin. In more severe cases, an *exchange transfusion* may be given to completely replace the infant's Rh^+ blood with Rh^-. In time, the infant's hemopoietic tissues will replace the donor's RBCs with Rh^+ cells, and by then the mother's antibody will have disappeared from the infant's blood.

Think About It

A baby with HDN typically has jaundice and an enlarged spleen. Explain these effects.

Other Blood Groups

In addition to the ABO and Rh groups, there are at least 100 other known blood groups with a total of more than 500 antigens, including the MN, Duffy, Kell, Kidd, and Lewis groups. These rarely cause transfusion reactions, but they are useful for such legal purposes as paternity and criminal cases and for research in anthropology and population genetics. The Kell, Kidd, and Duffy groups occasionally cause HDN.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

18. What are antibodies and antigens? How do they interact to cause a transfusion reaction?
19. What antibodies and antigens are present in people with each of the four ABO blood types?
20. Describe the cause, prevention, and treatment of HDN.
21. Why might someone be interested in determining a person's blood type other than ABO/Rh?

Leukocytes

Objectives

When you have completed this section, you should be able to

- state the general function that all leukocytes have in common;
- name and describe the five types of leukocytes; and
- describe the types, causes, and effects of abnormal leukocyte counts.

Leukocytes, or white blood cells (WBCs), play a number of roles in the body's defense against pathogens. Their individual functions are summarized in table 18.8, but they are discussed more extensively in chapter 21. There are five kinds of WBCs. They are easily distinguished from erythrocytes in stained blood films because they contain conspicuous nuclei that stain from light violet to dark purple with the most common blood stains. Three WBC types—the *neutrophils, eosinophils,* and *basophils*—are called **granulocytes** because their cytoplasm contains organelles that appear as colored granules through the microscope. These are missing or relatively scanty in the two types known as **agranulocytes**—the *lymphocytes* and *monocytes.*

Types of Leukocytes

The five leukocyte types are compared in table 18.8. From the photographs and data, take note of their sizes relative to each other and to the size of erythrocytes (which are about 7.5 μm in diameter). Also note how the leukocytes differ from each other in relative abundance—from neutrophils, which constitute about two-thirds of the WBC count, to basophils, which usually account for less than 1%. Nuclear shape is an important key to identifying leukocytes. The granulocytes are further distinguished from each other by the coarseness, abundance, and staining properties of their cytoplasmic granules.

Granulocytes

Neutrophils have very fine cytoplasmic granules that contain lysozyme, peroxidase, and other antibiotic agents. They are named for the way these granules take up blood stains at pH 7—some stain with acidic dyes and others with basic dyes, and the combined effect gives the cytoplasm a pale lilac color. The nucleus is usually divided into three to five lobes, which are connected by strands of nucleoplasm so delicate that the cell may appear to have multiple nuclei. Young neutrophils often exhibit an undivided nucleus shaped like a band or a knife puncture; they are thus called *band,* or *stab, cells.* Neutrophils are also called *polymorphonuclear* leukocytes (PMNs) because of their variety of nuclear shapes.

Eosinophils (EE-oh-SIN-oh-fills) are easily distinguished by their large rosy to orange-colored granules and prominent, usually bilobed nucleus.

In **basophils,** the nucleus is pale and usually hidden by the coarse, dark violet granules in the cytoplasm. It is sometimes difficult to distinguish a basophil from a lymphocyte, but basophils are conspicuously grainy while the lymphocyte nucleus is more homogeneous, and basophils lack the clear blue rim of cytoplasm usually seen in stained lymphocytes.

Agranulocytes

Lymphocytes are usually similar to erythrocytes in size, or only slightly larger. They are sometimes classified into three size classes (table 18.8), but there are gradations between these categories. Medium and large lymphocytes are usually seen in fibrous connective tissues and only occasionally in the circulating blood. In small lymphocytes, the nucleus often fills almost the entire cell and leaves only a narrow rim of clear, light blue cytoplasm. Large lymphocytes, however, have ample cytoplasm around the nucleus and are sometimes difficult to distinguish from monocytes. There are several subclasses of lymphocytes with different immune functions (see chapter 21), but they look alike through the light microscope.

Monocytes are the largest of the formed elements, typically about twice the diameter of an erythrocyte but sometimes approaching three times as large. The monocyte nucleus tends to stain a lighter blue than most leukocyte nuclei. The cytoplasm is abundant and relatively clear. In stained blood films monocytes sometimes appear as very large cells with bizarre stellate (star-shaped) or polygonal contours (see fig. 18.1*a*).

Abnormalities of Leukocyte Count

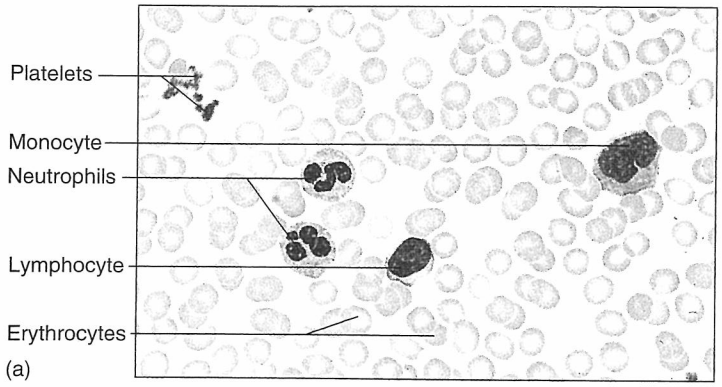
The total WBC count is normally 5,000 to 10,000 WBCs/μL. A count below this range, called **leukopenia**[19] (LOO-co-PEE-nee-uh), is seen in lead, arsenic, and mercury poisoning; radiation sickness; and such infectious

[19] *leuko* = white + *penia* = deficiency

useful than a total WBC count is a *differential WBC count,* which identifies what percentage of the total WBC count consists of each type of leukocyte. A high neutrophil count is a sign of bacterial infection; neutrophils become sharply elevated in appendicitis, for example. A high eosinophil count usually indicates an allergy or a parasitic infection such as hookworms or tapeworms.

Leukemia is a cancer of the hemopoietic tissues that usually produces an extraordinarily high number of circulating leukocytes and their precursors (fig. 18.19*b*). Leukemia is classified as myeloid or lymphoid, acute or chronic. **Myeloid leukemia** is marked by uncontrolled granulocyte production, whereas **lymphoid leukemia** involves uncontrolled lymphocyte or monocyte production. **Acute leukemia** appears suddenly, progresses rapidly, and causes death within a few months if it is not treated. **Chronic leukemia** develops more slowly and may go undetected for many months; if untreated, the typical survival time is about 3 years. Both myeloid and lymphoid leukemia occur in acute and chronic forms. The greatest success in treatment and cure has been with acute lymphoblastic leukemia, the most common type of childhood cancer. Treatment employs chemotherapy and marrow transplants along with the control of side effects such as anemia, hemorrhaging, and infection.

As leukemic cells proliferate, they replace normal bone marrow and a person suffers from a deficiency of normal granulocytes, erythrocytes, and platelets. Although enormous numbers of leukocytes are produced and spill over into the bloodstream, they are immature cells incapable of performing their normal defensive roles. The deficiency of competent WBCs leaves the patient vulnerable to *opportunistic infection*—the establishment of pathogenic organisms that usually cannot get a foothold in people with healthy immune systems. The RBC deficiency renders the patient anemic and fatigued, and the platelet deficiency results in hemorrhaging and impaired blood clotting. The immediate cause of death is usually hemorrhage or opportunistic infection. Cancerous hemopoietic tissue often metastasizes from the bone marrow or lymph nodes to other organs of the body, where the cells displace or compete with normal cells. Metastasis to the bone tissue itself is common and leads to bone and joint pain.



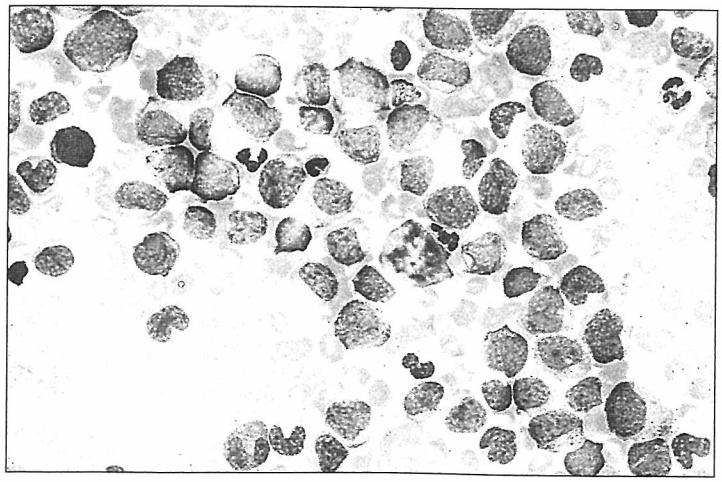

(b)

Figure 18.19 Normal and Leukemic Blood. (*a*) A normal blood smear; (*b*) blood from a patient with acute monocytic leukemia. Note the abnormally high number of white blood cells, especially monocytes, in *b*. **With all these extra white cells, why isn't the body's infection-fighting capability increased in leukemia?**

Before You Go On

Answer the following questions to test your understanding of the preceding section:

22. What is the overall function of leukocytes?
23. What can cause abnormally high or low leukocyte counts?
24. Define *leukemia.* Distinguish between myeloid and lymphoid leukemia.

Hemostasis—The Control of Bleeding

Objectives

When you have completed this section, you should be able to

- describe the body's mechanisms for controlling bleeding;
- list the functions of platelets;
- describe two reaction pathways that produce blood clots;
- explain what happens to blood clots when they are no longer needed;
- explain what keeps blood from clotting in the absence of injury; and
- describe some disorders of blood clotting.

Circulatory systems developed very early in animal evolution, and with them evolved mechanisms for stopping leaks, which are potentially fatal. **Hemostasis**[21] is the ces-

[21] *hemo* = blood + *stasis* = stability

sation of bleeding. Although hemostatic mechanisms may not stop a hemorrhage from a large blood vessel, they are quite effective at closing breaks in small ones. Platelets play multiple roles in hemostasis, so we begin with a consideration of their form and function.

Platelets

Platelets (see fig. 18.1) are not cells but small fragments of megakaryocyte cytoplasm. They are 2 to 4 μm in diameter and possess lysosomes, endoplasmic reticulum, a Golgi complex, and Golgi vesicles, or "granules," that contain a variety of factors involved in platelet function. Platelets have pseudopods and are capable of ameboid movement and phagocytosis. In normal blood from a fingerstick, the platelet count ranges from 130,000 to 400,000 platelets/μL (averaging about 250,000/μL). The count can vary greatly, however, under different physiological conditions and in blood from different places in the body. When a blood specimen dries on a slide, platelets clump together; therefore in stained blood films, they often appear in clusters.

Platelets have a broad range of functions, many of which have come to light only in recent years:

- They secrete *procoagulants,* or clotting factors, which promote blood clotting.
- They secrete vasoconstrictors, which cause *vascular spasms* in broken vessels.
- They form temporary *platelet plugs* to stop bleeding.
- They dissolve blood clots that have outlasted their usefulness.
- They phagocytize and destroy bacteria.
- They secrete chemicals that attract neutrophils and monocytes to sites of inflammation.
- They secrete growth factors that stimulate mitosis in fibroblasts and smooth muscle and help to maintain the linings of blood vessels.

There are three hemostatic mechanisms—*vascular spasm, platelet plug formation,* and *blood clotting (coagulation)* (fig. 18.20). Platelets play an important role in all three.

Vascular Spasm

The most immediate protection against blood loss is **vascular spasm,** a prompt constriction of the broken vessel. Several things trigger this reaction. An injury stimulates pain receptors, some of which directly innervate nearby blood vessels and cause them to constrict. This effect lasts only a few minutes, but other mechanisms take over by the time it subsides. Injury to the smooth muscle of the blood vessel itself causes a longer-lasting vasoconstriction, and platelets release serotonin, a chemical vasoconstrictor. Thus, the vascular spasm is maintained long enough for the other two hemostatic mechanisms to come into play.

Platelet Plug Formation

Platelets will not adhere to the endothelium (inner lining) of undamaged blood vessels. The endothelium is normally very smooth and coated with **prostacyclin,** a platelet repellent. When a vessel is broken, however, collagen

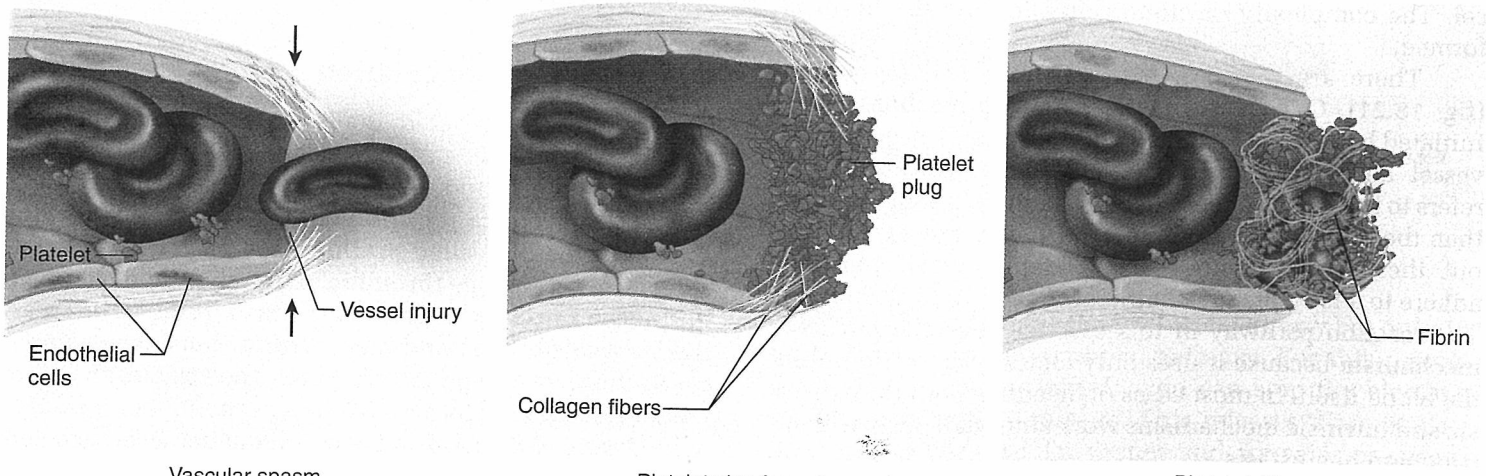


Figure 18.20 Hemostasis. (*a*) Vasoconstriction of a broken vessel reduces bleeding. (*b*) A platelet plug forms as platelets adhere to exposed collagen fibers of the vessel wall. The platelet plug temporarily seals the break. (*c*) A blood clot forms as platelets and erythrocytes become enmeshed in fibrin threads. This forms a longer-lasting seal and gives the vessel a chance to repair itself.
How does a clot differ from a platelet plug?

fibers of its wall are exposed to the blood. Upon contact with collagen or other rough surfaces, platelets put out long spiny pseudopods that adhere to the vessel and to other platelets; the pseudopods then contract and draw the walls of the vessel together. The mass of platelets thus formed, called a **platelet plug,** may reduce or stop minor bleeding.

As platelets aggregate, they undergo **degranulation**—the exocytosis of their cytoplasmic granules and release of factors that promote hemostasis. Among these are serotonin, a vasoconstrictor; adenosine diphosphate (ADP), which attracts more platelets to the area and stimulates their degranulation; and **thromboxane A_2,** an eicosanoid that promotes platelet aggregation, degranulation, and vasoconstriction. Thus, a positive feedback cycle is activated that can quickly seal a small break in a blood vessel.

Coagulation

Coagulation (clotting) of the blood is the last but most effective defense against bleeding. It is important for the blood to clot quickly when a vessel has been broken, but equally important for it not to clot in the absence of vessel damage. Because of this delicate balance, coagulation is one of the most complex processes in the body, involving over 30 chemical reactions. It is presented here in a very simplified form.

Perhaps clotting is best understood if we first consider its goal. The objective is to convert the plasma protein fibrinogen into **fibrin,** a sticky protein that adheres to the walls of a vessel. As blood cells and platelets arrive, they become stuck to the fibrin like insects sticking to a spider web (fig. 18.20). The resulting mass of fibrin, blood cells, and platelets ideally seals the break in the blood vessel. The complexity of clotting lies in how the fibrin is formed.

There are two reaction pathways to coagulation (fig. 18.21). One of them, the **extrinsic mechanism,** is initiated by clotting factors released by the damaged blood vessel and perivascular[22] tissues. The word *extrinsic* refers to the fact that these factors come from sources other than the blood itself. Blood may also clot, however, without these tissue factors—for example, when platelets adhere to a fatty plaque of atherosclerosis or to a test tube. The reaction pathway in this case is called the **intrinsic mechanism** because it uses only clotting factors found in the blood itself. In most cases of bleeding, both the extrinsic and intrinsic mechanisms work simultaneously to contribute to hemostasis.

Clotting factors (table 18.9) are called **procoagulants,** in contrast to the **anticoagulants** discussed later (see insight 18.5, p. 708). Most procoagulants are proteins produced by the liver. They are always present in the plasma in inactive form, but when one factor is activated, it functions as an enzyme that activates the next one in the pathway. That factor activates the next, and so on, in a sequence called a **reaction cascade**—a series of reactions, each of which depends on the product of the preceding one. Many of the clotting factors are identified by Roman numerals, which indicate the order in which they were discovered, not the order of the reactions. Factors IV and VI are not included in table 18.9. These terms were abandoned when it was found that factor IV was calcium and factor VI was activated factor V. The last four procoagulants in the table are called *platelet factors* (PF_1 through PF_4) because they are produced by the platelets.

Initiation of Coagulation

The extrinsic mechanism is diagrammed on the left side of figure 18.21. The damaged blood vessel and perivascular tissues release a lipoprotein mixture called **tissue thromboplastin[23] (factor III).** Factor III combines with factor VII to form a complex which, in the presence of Ca^{2+}, then activates factor X. The extrinsic and intrinsic pathways differ only in how they arrive at active factor X. Therefore, before examining their common pathway from factor X to the end, let's consider how the intrinsic pathway reaches this step.

The intrinsic mechanism is diagrammed on the right side of figure 18.21. Everything needed to initiate it is present in the plasma or platelets. When platelets degranulate, they release factor XII (Hageman factor, named for the patient in whom it was discovered). Through a cascade of reactions, this leads to activated factors XI, IX, and VIII, in that order—each serving as an enzyme that catalyzes the next step—and finally to factor X. This pathway also requires Ca^{2+} and PF_3.

Completion of Coagulation

Once factor X is activated, the remaining events are identical in the intrinsic and extrinsic mechanisms. Factor X combines with factors III and V in the presence of Ca^{2+} and PF_3 to produce *prothrombin activator.* This enzyme acts on a globulin called **prothrombin** (factor II) and converts it to the enzyme **thrombin.** Thrombin then chops up fibrinogen into shorter strands of fibrin. Factor XIII cross-links these fibrin strands to create a dense aggregation called *fibrin polymer,* which forms the structural framework of the blood clot.

Once a clot begins to form, it launches a self-accelerating positive feedback process that seals off the damaged vessel more quickly. Thrombin works with factor V to accelerate the production of prothrombin activator, which in turn produces more thrombin.

[22] *peri* = around + *vas* = vessel + *cular* = pertaining to

[23] *thrombo* = clot + *plast* = forming + *in* = substance

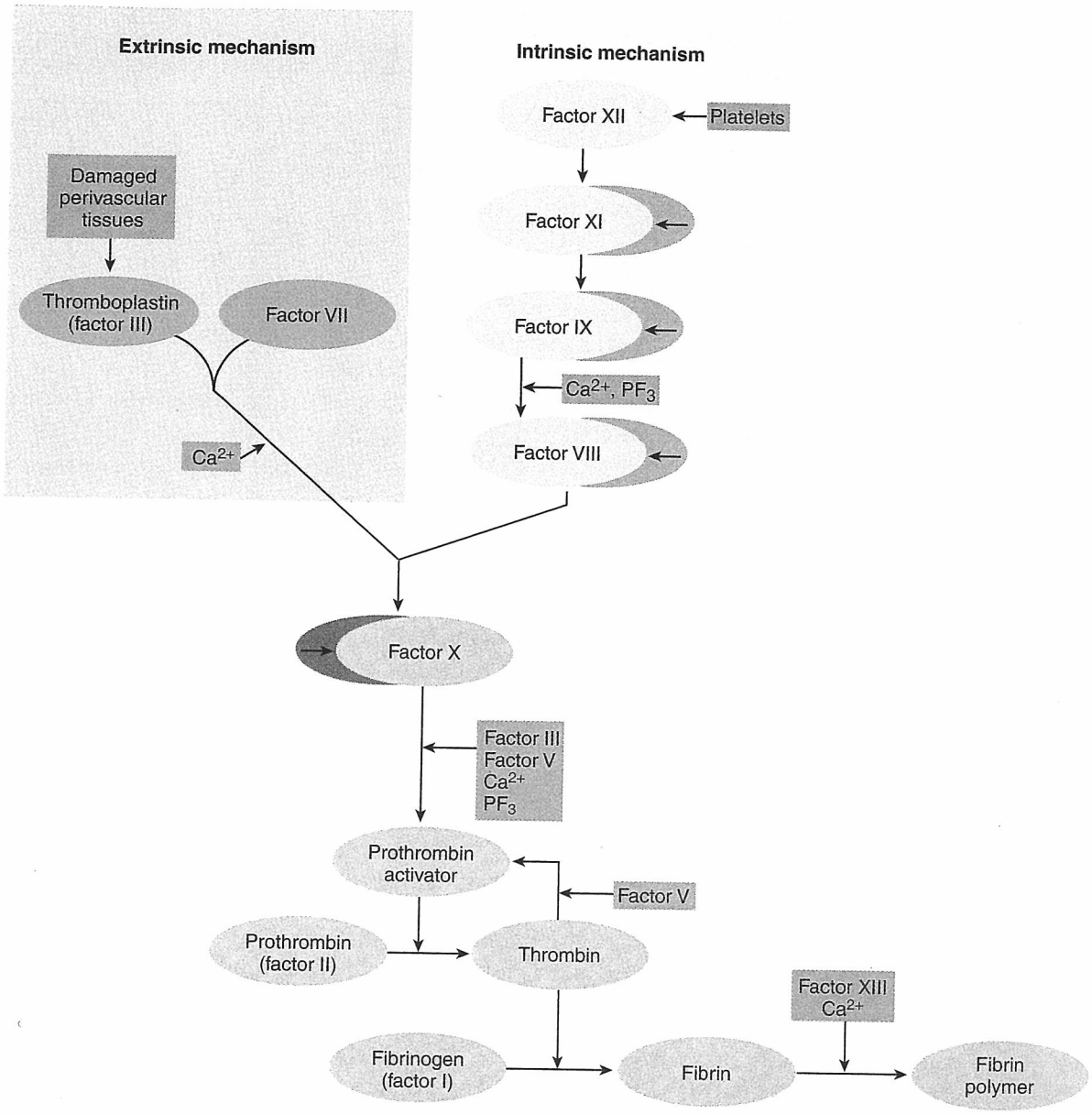


Figure 18.21 The Pathways of Coagulation. Most clotting factors act as enzymes that convert the next factor from an inactive form (*shaded ellipse*) to an active form (*lighter ellipse*).
Would hemophilia C (see p. 707) affect the extrinsic mechanism, the intrinsic mechanism, or both?

The cascade of enzymatic reactions acts as an amplifying mechanism to ensure the rapid clotting of blood (fig. 18.22). Each activated enzyme in the pathway produces a larger number of enzyme molecules at the following step. One activated molecule of factor XII at the start of the intrinsic pathway, for example, causes thousands of fibrin molecules to be produced very quickly. Note the similarity of this process to the *enzyme amplification* that occurs in hormone action (see chapter 17, fig. 17.21).

Notice that the extrinsic mechanism requires fewer steps to activate factor X than the intrinsic mechanism does; it is a "shortcut" to coagulation. It takes 3 to 6 minutes for a clot to form by the intrinsic pathway but only 15 seconds or so by the extrinsic pathway. For this reason, when a small wound bleeds, you can stop the bleeding sooner by massaging the site. This releases thromboplastin from the perivascular tissues and activates or speeds up the extrinsic pathway.

A number of laboratory tests are used to evaluate the efficiency of coagulation. Normally, the bleeding of a fingerstick should stop within 2 to 3 minutes, and a sample of blood in a clean test tube should clot within 15 minutes. Other techniques are available that can separately assess the effectiveness of the intrinsic and extrinsic mechanisms.

Table 18.9 Clotting Factors (Procoagulants)

Number	Name	Origin	Function
I	Fibrinogen	Liver	Precursor of fibrin
II	Prothrombin	Liver	Precursor of thrombin
III	Tissue thromboplastin	Perivascular tissue	Activates factor VII
V	Proaccelerin	Liver	Activates factor VII; combines with factor X to form prothrombin activator
VII	Proconvertin	Liver	Activates factor X in extrinsic pathway
VIII	Antihemophiliac factor A	Liver	Activates factor X in intrinsic pathway
IX	Antihemophiliac factor B	Liver	Activates factor VIII
X	Thrombokinase	Liver	Combines with factor V to form prothrombin activator
XI	Antihemophiliac factor C	Liver	Activates factor IX
XII	Hageman factor	Liver, platelets	Activates factor XI and plasmin; converts prekallikrein to kallikrein
XIII	Fibrin-stabilizing factor	Platelets, plasma	Cross-links fibrin filaments to make fibrin polymer and stabilize clot
PF_1	Platelet factor 1	Platelets	Same role as factor V; also accelerates platelet activation
PF_2	Platelet factor 2	Platelets	Accelerates thrombin formation
PF_3	Platelet factor 3	Platelets	Aids in activation of factor VIII and prothrombin activator
PF_4	Platelet factor 4	Platelets	Binds heparin during clotting to inhibit its anticoagulant effect

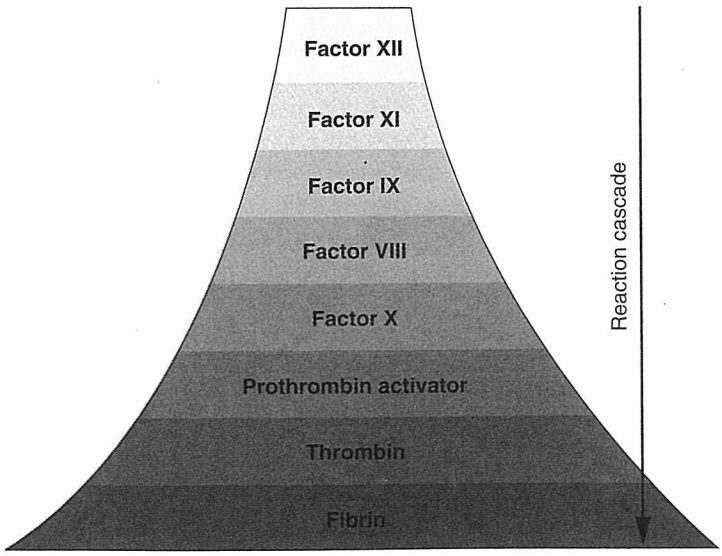


Figure 18.22 Enzyme Amplification in Blood Clotting. Each clotting factor produces many molecules of the next one, so the number of active clotting factors increases rapidly and a large amount of fibrin is quickly formed. The example shown here is for the intrinsic mechanism.

The Fate of Blood Clots

After a clot has formed, spinous pseudopods of the platelets adhere to strands of fibrin and contract. This pulls on the fibrin threads and draws the edges of the broken vessel together, like a drawstring closing a purse. Through this process of **clot retraction,** the clot becomes more compact within about 30 minutes.

Platelets and endothelial cells secrete a mitotic stimulant named *platelet-derived growth factor (PDGF).* PDGF stimulates fibroblasts and smooth muscle cells to multiply and repair the damaged blood vessel. Fibroblasts also invade the clot and produce fibrous connective tissue, which helps to strengthen and seal the vessel while the repairs take place.

Eventually, tissue repair is completed and the clot must be disposed of. **Fibrinolysis,** the dissolution of a clot, is achieved by a small cascade of reactions with a positive feedback component. In addition to promoting clotting, factor XII catalyzes the formation of a plasma enzyme called **kallikrein** (KAL-ih-KREE-in). Kallikrein, in turn, converts the inactive protein *plasminogen* into **plasmin,** a fibrin-dissolving enzyme that breaks up the clot. Thrombin also activates plasmin, and plasmin indirectly promotes the formation of more kallikrein, thus completing a positive feedback loop (fig. 18.23).

Prevention of Inappropriate Coagulation

Precise controls are required to prevent coagulation when it is not needed. These include the following:

- **Platelet repulsion.** As noted earlier, platelets do not adhere to the smooth prostacyclin-coated endothelium of undamaged blood vessels.

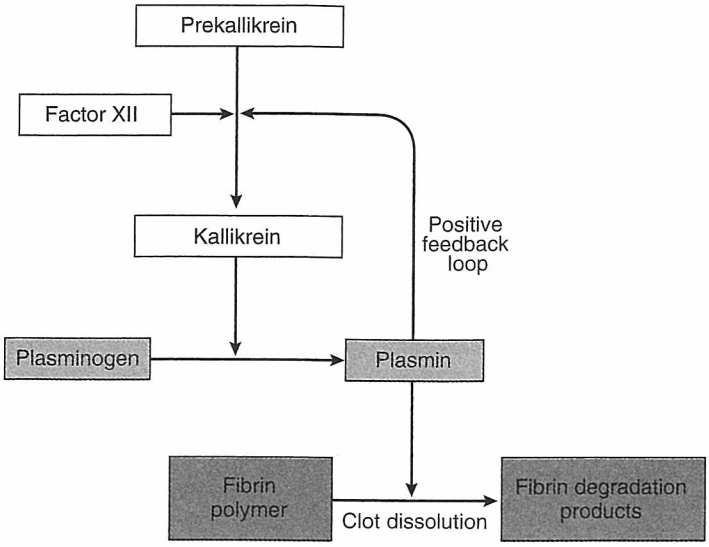


Figure 18.23 The Mechanism for Dissolving Blood Clots. Prekallikrein is converted to kallikrein. Kallikrein is an enzyme that catalyzes the formation of plasmin. Plasmin is an enzyme that dissolves the blood clot.

- **Dilution.** Small amounts of thrombin form spontaneously in the plasma, but at normal rates of blood flow the thrombin is diluted so quickly that a clot has little chance to form. If flow decreases, however, enough thrombin can accumulate to cause clotting. This can happen in circulatory shock, for example, when output from the heart is diminished and circulation slows down.
- **Anticoagulants.** Thrombin formation is suppressed by anticoagulants that are present in the plasma. **Antithrombin,** secreted by the liver, deactivates thrombin before it can act on fibrinogen. **Heparin,** secreted by basophils and mast cells, interferes with the formation of prothrombin activator, blocks the action of thrombin on fibrinogen, and promotes the action of antithrombin. Heparin is given by injection to patients with abnormal clotting tendencies.

Coagulation Disorders

In a process as complex as coagulation, it is not surprising that things can go wrong. Clotting deficiencies can result from causes as diverse as malnutrition, leukemia, and gallstones (see insight 18.4).

A deficiency of any clotting factor can shut down the coagulation cascade. This happens in **hemophilia,** a family of hereditary diseases characterized by deficiencies of one factor or another. Because of its sex-linked recessive mechanism of heredity, most hemophilia occurs predominantly in males. They can inherit it only from their mothers, however, as happened with the descendants of Queen Victoria. The lack of factor VIII causes *classical hemophilia (hemophilia A),* which accounts for about 83% of cases and afflicts 1 in 5,000 males worldwide. Lack of factor IX causes *hemophilia B,* which accounts for 15% of cases and occurs in about 1 out of 30,000 males. Factors VIII and IX are therefore known as *antihemophilic factors A* and *B.* A rarer form called *hemophilia C* (factor XI deficiency) is autosomal, not sex-linked, so it occurs equally in both sexes.

Before purified factor VIII became available in the 1960s, more than half of those with hemophilia died before age 5 and only 10% lived to age 21. Physical exertion causes bleeding into the muscles and joints. Excruciating pain and eventual joint immobility can result from intramuscular and joint **hematomas**[24] (masses of clotted blood in the tissues). Hemophilia varies in severity, however. Half of the normal level of clotting factor is enough to prevent the symptoms, and the symptoms are mild even in individuals with as little as 30% of the normal amount. Such cases may go undetected even into adulthood. Bleeding can be relieved for a few days by transfusion of plasma or purified clotting factors.

Think About It

Why is it important for people with hemophilia not to use aspirin? (Hint: See p. 666.)

Insight 18.4 Clinical Application

Liver Disease and Blood Clotting

Proper blood clotting depends on normal liver function for two reasons. First, the liver synthesizes most of the clotting factors. Therefore, diseases such as hepatitis, cirrhosis, and cancer that degrade liver function result in a deficiency of clotting factors. Second, the synthesis of clotting factors II, VII, IX, and X require vitamin K. The absorption of vitamin K from the diet requires bile, a liver secretion. Gallstones can lead to a clotting deficiency by obstructing the bile duct and thus interfering with bile secretion and vitamin K absorption. Efficient blood clotting is especially important in childbirth, since both the mother and infant bleed from the trauma of birth. Therefore, pregnant women should take vitamin K supplements to ensure fast clotting, and newborn infants may be given vitamin K injections.

Far more people die from unwanted blood clotting than from clotting failure. Most strokes and heart attacks are due to **thrombosis**—the abnormal clotting of blood in an unbroken vessel. A **thrombus** (clot) may grow large enough to obstruct a small vessel, or a piece of it may break loose and begin to travel in the bloodstream as an **embolus.**[25] An embolus may lodge in a small artery and block blood flow

[24] *hemat* = blood + *oma* = mass
[25] *em* = in, within + *bolus* = ball, mass

from that point on. If that vessel supplies a vital organ such as the heart, brain, lung, or kidney, *infarction* (tissue death) may result. About 650,000 Americans die annually of *thromboembolism* (traveling blood clots) in the cerebral, coronary, and pulmonary arteries.

Thrombosis is more likely to occur in veins than in arteries because blood flows more slowly in the veins and does not dilute thrombin and fibrin as rapidly. It is especially common in the leg veins of inactive people and patients immobilized in a wheelchair or bed. Most venous blood flows directly to the heart and then to the lungs. Therefore, blood clots arising in the legs or arms commonly lodge in the lungs and cause *pulmonary embolism*. When blood cannot circulate freely through the lungs, it cannot receive oxygen and a person may die of hypoxia.

Table 18.10 describes some additional disorders of the blood. The effects of aging on the blood are described on pages 1110 to 1111.

Before You Go On

Answer the following questions to test your understanding of the preceding section:

25. What are the three basic mechanisms of hemostasis?
26. How do the extrinsic and intrinsic mechanisms of coagulation differ? What do they have in common?
27. In what respect does blood clotting represent a negative feedback loop? What part of it is a positive feedback loop?
28. Describe some of the mechanisms that prevent clotting in undamaged vessels.
29. Describe a common source and effect of pulmonary embolism.

Insight 18.5 Clinical Application

Controlling Coagulation

For many cardiovascular patients, the goal of treatment is to prevent clotting or to dissolve clots that have already formed. Several strategies employ inorganic salts and products of bacteria, plants, and animals with anticoagulant and clot-dissolving effects.

Preventing Clots from Forming

Since calcium is an essential requirement for blood clotting, blood samples can be kept from clotting by adding a few crystals of sodium oxalate, sodium citrate, or EDTA[26]—salts that bind calcium ions and prevent them from participating in the coagulation reactions. Blood-collection equipment such as hematocrit tubes may also be coated with heparin, a natural anticoagulant whose action was explained earlier.

Since vitamin K is required for the synthesis of clotting factors, anything that antagonizes vitamin K usage makes the blood clot less readily. One vitamin K antagonist is *coumarin*[27] (COO-muh-rin), a sweet-smelling extract of tonka beans, sweet clover, and other plants, used in perfume. Taken orally by patients at risk for thrombosis, coumarin takes up to 2 days to act, but it has longer-lasting effects than heparin. A similar vitamin K antagonist is the pharmaceutical preparation *Warfarin*[28] *(Coumadin),* which was originally developed as a pesticide—it makes rats bleed to death. Obviously, such anticoagulants must be used in humans with great care.

As explained in chapter 17, aspirin suppresses the formation of prostaglandins including thromboxane A_2, a factor in platelet aggregation. Low daily doses of aspirin can therefore suppress thrombosis and prevent heart attacks.

Many parasites feed on the blood of vertebrates and secrete anticoagulants to keep the blood flowing. Among these are segmented

Chapter 18

Table 18.10 Some Disorders of the Blood

Infectious mononucleosis	Infection of B lymphocytes with Epstein-Barr virus, most commonly in adolescents and young adults. Usually transmitted by exchange of saliva, as in kissing. Causes fever, fatigue, sore throat, inflamed lymph nodes, and leukocytosis. Usually self-limiting and resolves within a few weeks.
Thalassemia	A group of hereditary anemias most common in Greeks, Italians, and others of Mediterranean descent; shows a deficiency or absence of α or β hemoglobin and RBC counts that may be less than 2 million/μL.
Thrombocytopenia	A platelet count below 100,000/μL. Causes include bone marrow destruction by radiation, drugs, poisons, or leukemia. Signs include small hemorrhagic spots in the skin or hematomas in response to minor trauma.
Disseminated intravascular coagulation (DIC)	Widespread clotting within unbroken vessels, limited to one organ or occurring throughout the body. Usually triggered by septicemia but also occurs when blood circulation slows markedly (as in cardiac arrest). Marked by widespread hemorrhaging, congestion of the vessels with clotted blood, and tissue necrosis in blood-deprived organs.
Septicemia	Bacteremia (bacteria in the bloodstream) accompanying infection elsewhere in the body. Often causes fever, chills, and nausea, and may cause DIC or septic shock. (see p. 765)

Disorders described elsewhere

Anemia 692
Embolism 708
Hematoma 198, 707
Hemolytic disease of the newborn 697
Hemophilia 707
Hypoproteinemia 682
Hypoxemia 685
Leukemia 702
Leukocytosis 701
Leukopenia 699
Polycythemia 692
Sickle-cell disease 693
Thrombosis 707
Transfusion reaction 696

worms known as leeches. Leeches secrete a local anesthetic that makes their bites painless; therefore, as early as 1567 B.C.E., physicians used them for bloodletting. This method was less painful and repugnant to their patients than *phlebotomy*[29]—cutting a vein—and indeed, leeching became very popular. In seventeenth-century France it was quite the rage; tremendous numbers of leeches were used to treat headaches, insomnia, whooping cough, obesity, tumors, menstrual cramps, mental illness, and almost anything else doctors or their patients imagined to be caused by "bad blood."

The first known anticoagulant was discovered in the saliva of the medicinal leech, *Hirudo medicinalis,* in 1884. Named *hirudin,* it is a polypeptide that prevents clotting by inhibiting thrombin. It causes the blood to flow freely while the leech feeds and for as long as an hour thereafter. While the doctrine of bad blood is now discredited, leeches have lately reentered medical usage (fig. 18.24). A major problem in reattaching a severed body part such as a finger or ear is that the tiny veins draining these organs are too small to reattach surgically. Since arterial blood flows into the reattached organ and cannot flow out, it pools and clots there. This inhibits the regrowth of veins and the flow of fresh blood through the organ and thus often leads to necrosis. Some vascular surgeons now place leeches on the reattached part. Their anticoagulant keeps the blood flowing freely and allows new veins to grow. After 5 to 7 days, venous drainage is restored and leeching can be stopped.

Anticoagulants also occur in the venom of some snakes. *Arvin,* for example, is obtained from the venom of the Malayan viper. It rapidly breaks down fibrinogen and may have potential as a clinical anticoagulant.

Dissolving Clots That Have Already Formed

When a clot has already formed, it can be treated with clot-dissolving drugs such as *streptokinase,* an enzyme made by certain bacteria (streptococci). Intravenous streptokinase is used to dissolve blood clots in coronary vessels, for example. It is nonspecific, however, and digests almost any protein. *Tissue plasminogen activator (TPA)* works faster, is more specific, and is now made by transgenic bacteria. TPA converts plasminogen into the clot-dissolving enzyme plasmin. Some anticoagulants of animal origin also work by dissolving fibrin. A giant Amazon leech, *Haementeria,* produces one such anticoagulant named *hementin.* This, too, has been successfully produced by genetically engineered bacteria and used to dissolve blood clots in cardiac patients.

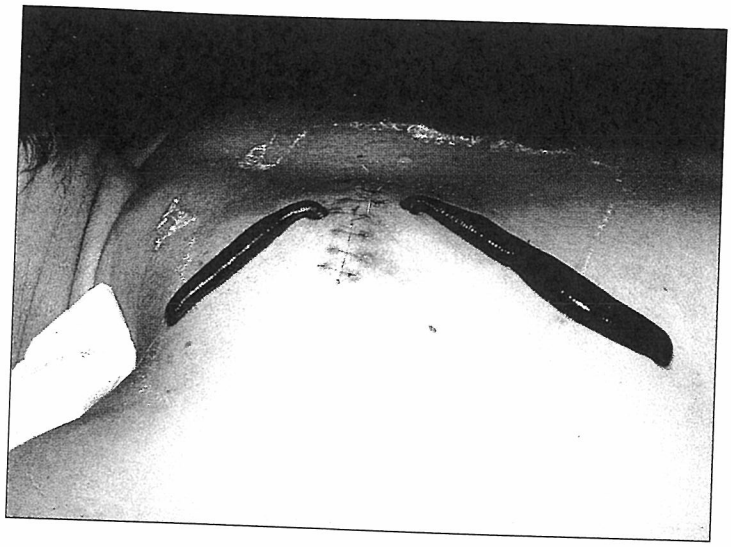


Figure 18.24 A Modern Use of Leeching. Two medicinal leeches are being used to remove clotted blood from a postsurgical hematoma. These leeches grow up to 20 cm long.

[26] ethylenediaminetetraacetic acid
[27] *coumarú,* tonka bean tree
[28] acronym from Wisconsin Alumni Research Foundation
[29] *phlebo* = vein + *tomy* = cutting

Chapter Review

Review of Key Concepts

Functions and Properties of Blood (p. 680)

1. Blood serves to transport O_2, CO_2, nutrients, wastes, hormones, and heat; it protects the body by means of antibodies, leukocytes, platelets, and its roles in inflammation; and it helps to stabilize the body's water balance and fluid pH.
2. Blood is about 55% *plasma* and 45% *formed elements* by volume.
3. The formed elements include erythrocytes, platelets, and five kinds of leukocytes.
4. The viscosity of blood, stemming mainly from its RBCs and proteins, is an important factor in blood flow.
5. The osmolarity of blood, stemming mainly from its RBCs, proteins, and Na^+, governs its water content and is thus a major factor in blood volume and pressure. The protein contribution to osmolarity is the *colloid osmotic pressure.*

Plasma (p. 683)

1. Protein is the most abundant plasma solute by weight. The three major plasma proteins are albumins, globulins, and fibrinogen.
2. The liver produces all the plasma proteins except γ globulins (antibodies), which are produced by *plasma cells.*
3. Nonprotein nitrogenous substances in the plasma include amino acids and nitrogenous wastes. The most abundant nitrogenous waste is *urea.*
4. Nutrients carried in the plasma include glucose, amino acids, fats, cholesterol, phospholipids, vitamins, and minerals.