Alterations in Red Blood Cells

Although the lungs provide the means for gas exchange between the external and internal environment, it is the hemoglobin in the red blood cells that transports oxygen to the tissues. The red blood cells also function as carriers of carbon dioxide and participate in acid-base balance. The function of the red blood cells, in terms of oxygen transport, is discussed in Chapter 19, and acid-base balance is covered in Chapter 6. This chapter focuses on the red blood cell, anemia, and polycythemia.

THE RED BLOOD CELL

The mature red blood cell, the erythrocyte, is a non-nucleated, biconcave disk (Fig. 13-1). This shape increases the surface area available for diffusion of oxygen and allows the cell to change in volume and shape without rupturing its membrane. A cytoskeleton of proteins attached to the lipid bilayer provides this unique shape and flexibility. The biconcave form presents the plasma with a surface 20 to 30 times greater than if the red blood cell were an absolute sphere. The erythrocytes, 500 to 1000 times more numerous than other blood cells, are the most common type of blood cell.

The function of the red blood cell, facilitated by the hemoglobin molecule, is to transport oxygen to the tissues. Hemoglobin also binds some carbon dioxide and carries it from the tissues to the lungs. The hemoglobin molecule is composed of two pairs of structurally different polypeptide chains determined by genes (Fig. 13-2). Alterations in these genes can result in abnormal hemoglobins. Each of the four polypeptide chains is attached to a *heme* unit, which surrounds an atom of iron that binds oxygen. Thus, one molecule of hemoglobin can carry four molecules of oxygen.

The two major types of normal hemoglobin are adult hemoglobin (HbA) and fetal hemoglobin (HbF). HbA consists of a pair of α chains and a pair of β chains. HbF is the predominant hemoglobin in the fetus from the third through the ninth month of gestation. It has a pair of γ chains substituted for the β chains. Because of this chain substitution, HbF has a high affinity for oxygen. This facilitates the transfer of oxygen across the placenta. HbF is replaced within 6 months of birth with HbA.

The rate at which hemoglobin is synthesized depends on the availability of iron for heme synthesis. A lack of iron results in relatively small amounts of hemoglobin in the red blood cells. The amount of iron in the body is approximately 35 to 50 mg/kg of body weight for males and less for females. Body iron is found in several compartments. Most of the functional iron (80%) is found in hemoglobin, with small amounts being found in the myoglobin of muscle, the cytochromes, and iron-containing enzymes such as catalase. Approximately 15% to 20% is stored in the bone marrow, liver, spleen, and other organs. Iron in the hemoglobin compartment is recycled. As red

■ **FIGURE 13-1** ■ Scanning micrograph of normal red blood cells shows their normal concave appearance (× 3000). (© Andrew Syred, Science Photo Lab, Science Source/Photo Researchers)
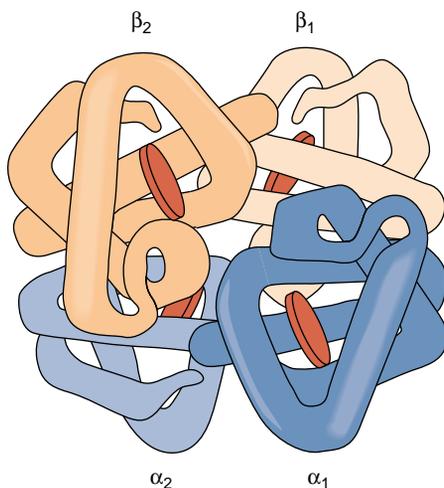

■ **FIGURE 13-3** ■ Iron cycle.

blood cells age and are destroyed in the spleen, iron from their hemoglobin is released into the circulation and transported to the bone marrow for use in production of new red cells or to the liver and other tissues for storage.

Dietary iron helps to maintain body stores. Iron, principally derived from meat, is absorbed in the small intestine, especially the duodenum (Fig. 13-3). When body stores of iron are diminished or red cell production is stimulated, absorption is increased. In iron overload, excretion of iron is accelerated. Normally, some iron is sequestered in the intestinal epithelial cells and is lost in the feces as these cells slough. The iron that is absorbed enters the circulation, where it immediately combines with a β-globulin, called *apotransferrin*, to form *transferrin*, which is then transported in the plasma. From the plasma, iron can be deposited in tissues such as the liver. There it is stored as *ferritin*, a protein–iron complex, which can easily return to the circulation. Serum
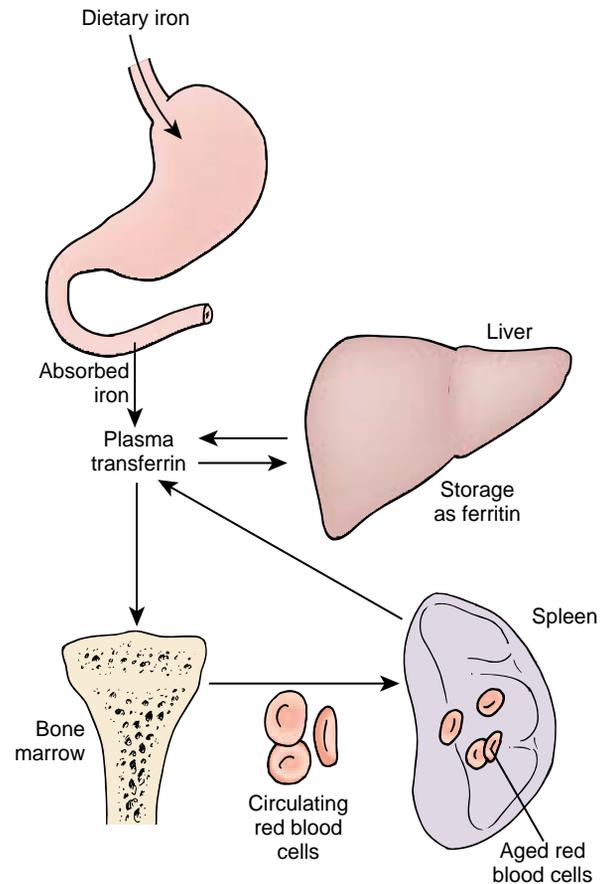
ferritin levels, which can be measured in the laboratory, provide an index of body iron stores. Clinically, decreased serum ferritin levels indicate the need for prescription of iron supplements. Transferrin can also deliver iron to the developing red cell in bone marrow by binding to membrane receptors. The iron is taken up by the developing red cell, where it is used in heme synthesis.

Red Cell Production

Erythropoiesis is the production of red blood cells. After birth, red cells are produced in the red bone marrow. Until age 5 years, almost all bones produce red cells to meet growth needs. After this period, bone marrow activity gradually declines. After 20 years of age, red cell production takes place mainly in the membranous bones of the vertebrae, sternum, ribs, and pelvis. With this reduction in activity, the red bone marrow is replaced with fatty yellow bone marrow.

The red cells are derived from the erythroblasts or red cell precursors, which are continuously being formed from the pluripotent stem cells in the bone marrow (Fig. 13-4). As they develop into mature red cells, the red cell precursors move through a series of divisions, each producing a smaller cell. Hemoglobin synthesis begins at an early stage and continues until the cell becomes a mature erythrocyte. During the maturation time, the red blood cell accumulates hemoglobin as the

■ **FIGURE 13-2** ■ Structure of the hemoglobin molecule, showing the four subunits.

nucleus condenses and is finally lost. The period from stem cell to emergence of the reticulocyte in the circulation normally takes approximately 1 week. Maturation of reticulocyte to erythrocyte takes approximately 24 to 48 hours. During this process, the red cell loses its mitochondria and ribosomes, along with its ability to produce hemoglobin and engage in oxidative metabolism. Most maturing red cells enter the blood as reticulocytes. Approximately 1% of the body's total complement of red blood cells is generated from bone marrow each day, so the reticulocyte count serves as an index of the erythropoietic activity of the bone marrow.

Erythropoiesis is governed for the most part by tissue oxygen needs. Any condition that causes a decrease in the amount of oxygen that is transported in the blood produces an increase in red cell production. The oxygen content of the blood does not act directly on the bone marrow to stimulate red blood cell production. Instead, the decreased oxygen content is sensed by the kidneys, which then produce a hormone called *erythropoietin*. Normally, the kidneys produce approximately 90% of erythropoietin, with the remaining 10% being released by the liver. In the absence of erythropoietin, as in kidney failure, hypoxia has little or no effect on red blood cell production. Erythropoietin takes several days to effect a release of red blood cells from the bone marrow, and only after 5 days or more does red blood cell production reach a maximum.

Erythropoietin acts in the bone marrow by binding to receptors on committed stem cells. It functions on many levels to promote hemoglobin synthesis, increase production of membrane proteins, and cause differentiation of erythroblasts. Human erythropoietin can be produced by recombinant deoxyribonucleic acid (DNA) technology. It is used for management of anemia in cases of chronic renal failure, for treatment of chemotherapy-induced anemia in persons with malignancies, and treatment of anemia in persons with human immunodeficiency virus (HIV) infection who are being treated with zidovudine.

Because red blood cells are released into the blood as reticulocytes, the percentage of these cells is higher when there is a marked increase in red blood cell production. For example, in some severe anemias, the reticulocytes may account for as much as 30% of the total red cell count. In some situations, red cell production is so accelerated that numerous erythroblasts appear in the blood.
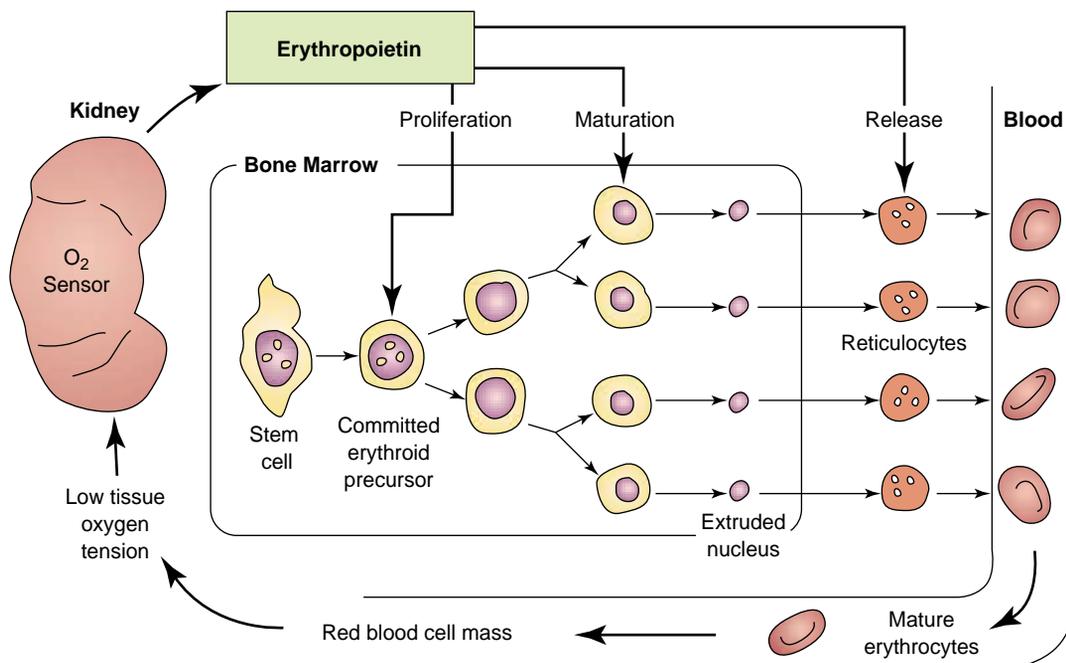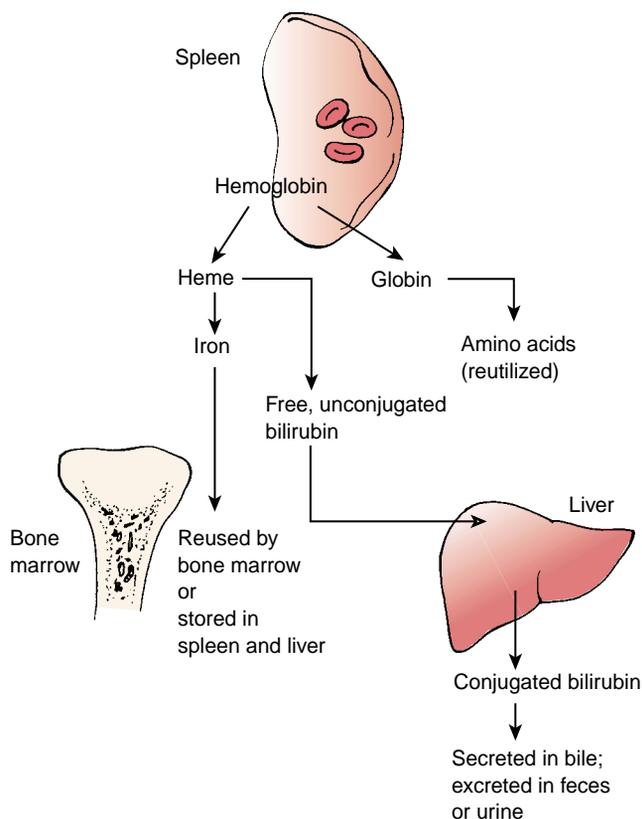

■ **FIGURE 13-4** ■ Red blood cell development.

Red Cell Destruction

Mature red blood cells have a life span of approximately 4 months or 120 days. As the red blood cell ages, a number of changes occur. Metabolic activity in the cell decreases, and enzyme activity decreases; adenosine triphosphate (ATP) decreases, and the cell membrane becomes more fragile. Once the red cell membrane becomes fragile, the cell ruptures during passage through narrowed places in the circulation. Many of the red cells self-destruct in the small trabecular spaces in the red pulp of the spleen. The rate of red cell destruction (1% per day) normally is equal to red cell production, but in conditions such as hemolytic anemia, the cell's life span may be shorter.

The destruction of red blood cells is facilitated by a group of large phagocytic cells found in the spleen, liver, bone marrow, and lymph nodes. These phagocytic cells ingest the hemoglobin from the ruptured cells and break it down in a series of enzymatic reactions. During these reactions, the amino acids from the globulin chains and iron from the heme units are salvaged and reused (Fig. 13-5). The bulk of the heme unit is converted to bilirubin, the pigment of bile, which is insoluble in plasma and attaches to the plasma proteins for transport. Bilirubin is removed from the blood by the liver and conjugated with glucuronide to render it water soluble so that it can be excreted in the bile. The plasma-insoluble form of bilirubin is referred to as *unconjugated bilirubin;* the water-soluble form is referred to as *conjugated bilirubin.* Serum levels of conjugated and unconjugated bilirubin can be measured in the laboratory and are reported as direct and indirect, respectively. If red cell destruction and consequent bilirubin production are excessive, unconjugated bilirubin accumulates in the blood. This results in a yellow discoloration of the skin, called *jaundice.*

When red blood cell destruction takes place in the circulation, as in hemolytic anemia, the hemoglobin remains in the plasma. The plasma contains a hemoglobin-binding protein called *haptoglobin.* Other plasma proteins, such as albumin, can also bind hemoglobin. With extensive intravascular destruction of red blood cells, hemoglobin levels may exceed the hemoglobin-binding capacity of haptoglobin. When this happens, free hemoglobin appears in the blood (*i.e.,* hemoglobinemia) and is excreted in the urine (*i.e.,* hemoglobinuria). Because excessive red blood cell destruction can occur in hemolytic transfusion reactions, urine samples are tested for free hemoglobin after a transfusion reaction.

Red Cell Metabolism and Hemoglobin Oxidation

The red blood cell, which lacks mitochondria, relies on glucose and the glycolytic pathway for its metabolic needs. The enzyme-mediated anaerobic metabolism of glucose generates the ATP needed for normal membrane function and ion transport. The depletion of glucose or the functional deficiency of one of the glycolytic enzymes leads to the premature death of the red blood cell. An offshoot of the glycolytic pathway is the production of 2,3-diphosphoglycerate (2,3-DPG), which binds to the hemoglobin molecule and reduces the affinity of hemoglobin for oxygen. This facilitates the release of oxygen at the tissue level. An increase in the concentration of 2,3-DPG occurs in conditions of chronic hypoxia such as chronic lung disease, anemia, and high altitudes.

The oxidation of hemoglobin—the combining of hemoglobin with oxygen—can be interrupted by certain chemicals (*e.g.,* nitrates and sulfates) and drugs that oxidize hemoglobin to an inactive form. For example, the nitrite ion reacts with hemoglobin to produce *methemoglobin*, which has a low affinity for oxygen. Large doses of nitrites can result in high levels of methemoglobin, causing pseudocyanosis and tissue hypoxia. For example, sodium nitrate, which is used in curing meats, can produce methemoglobin when taken in large amounts. In nursing infants, the intestinal flora is capable of converting significant amounts of inorganic nitrate (*e.g.,* from well water) to nitrite. A hereditary deficiency of glucose 6-phosphate dehydrogenase (G6PD; to be discussed) predisposes to oxidative denaturation of hemoglobin, with resultant red cell injury and lysis. Hemolysis occurs as the result of oxidative stress generated by either an infection or exposure to certain drugs.

Laboratory Tests

Red blood cells can be studied by means of a sample of blood (Table 13-1). In the laboratory, automated blood cell counters rapidly provide accurate measurements of red cell content and cell indices. The *red blood cell count* (RBC) measures the total number of red blood cells in 1 mm³ of blood. The *percentage of reticulocytes* (normally approximately 1%) provides an index of the rate of red cell production. The *hemoglobin* (grams per 100 mL of blood) measures the hemoglobin content of the blood. The major components of blood are the red cell mass and plasma volume. The *hematocrit* measures the volume of red

Spleen

Hemoglobin

Heme — Globin

Iron

Amino acids (reutilized)

Free, unconjugated bilirubin

Bone marrow

Reused by bone marrow or stored in spleen and liver

Liver

Conjugated bilirubin

Secreted in bile; excreted in feces or urine

■ **FIGURE 13-5** ■ Destruction of red blood cells and fate of hemoglobin.

TABLE 13-1	Standard Laboratory Values for Red Blood Cells	
Test	**Normal Values**	**Significance**
Red blood cell count (RBC)		
Men	$4.2–5.4 \times 10^6/\mu L$	Number of red cells in the blood
Women	$3.6–5.0 \times 10^6/\mu L$	
Reticulocytes	1.0%–1.5% of total RBC	Rate of red cell production
Hemoglobin		
Men	14–16.5 g/dL	Hemoglobin content of the blood
Women	12–15 g/dL	
Hematocrit		
Men	40%–50%	Volume of cells in 100 mL of blood
Women	37%–47%	
Mean corpuscular volume	85–100 fL/red cell	Size of the red cell
Mean corpuscular hemoglobin concentration	31–35 g/dL	Concentration of hemoglobin in the red cell
Mean cell hemoglobin	27–34 pg/cell	Red cell mass

cell mass in 100 mL of plasma volume. To determine the hematocrit, a sample of blood is placed in a glass tube, which is then centrifuged to separate the cells and the plasma. The hematocrit may be deceptive because it varies with the quantity of extracellular fluid, rising with dehydration and falling with overexpansion of extracellular fluid volume.

Red cell indices are used to differentiate types of anemias by size or color of red cells. The *mean corpuscular volume* (MCV) reflects the volume or size of the red cells. The MCV falls in microcytic (small cell) anemia and rises in macrocytic (large cell) anemia. Some anemias are normocytic (*i.e.,* cells are of normal size or MCV). The *mean corpuscular hemoglobin concentration* (MCHC) is the concentration of hemoglobin in each cell. Hemoglobin accounts for the color of red blood cells. Anemias are described as *normochromic* (normal color or MCHC) or *hypochromic* (decreased color or MCHC). *Mean cell hemoglobin* (MCH) refers to the mass of the red cell and is less useful in classifying anemias.

A stained blood smear provides information about the size, color, and shape of red cells and the presence of immature or abnormal cells. If blood smear results are abnormal, examination of the bone marrow may be important. Marrow commonly is aspirated with a special needle from the posterior iliac crest or the sternum. The aspirate is stained and observed for number and maturity of cells and abnormal types.

In summary, the red blood cell provides the means for transporting oxygen from the lungs to the tissues. Red cells develop from stem cells in the bone marrow and are released as reticulocytes into the blood, where they become mature erythrocytes. Red blood cell production is regulated by the hormone erythropoietin, which is produced by the kidney in response to a decrease in oxygen levels. The life span of a red blood cell is approximately 120 days. Red cell destruction normally occurs in the spleen, liver, bone marrow, and lymph nodes. In the process of destruction, the iron from the hemoglobin is returned to the bone marrow for reuse in red cell production or taken to the liver or other tissues for storage. The heme portion of the hemoglobin molecule is converted to bilirubin. Bilirubin, which is insoluble in plasma, attaches to plasma proteins for transport in the blood. It is removed from the blood by the liver and conjugated to a water-soluble form so that it can be excreted in the bile.

The red blood cell, which lacks mitochondria, relies on glucose and the glycolytic pathway for its metabolic needs. The end-product of the glycolytic pathway, 2,3-DPG, increases the release of oxygen to the tissues during conditions of hypoxia by reducing hemoglobin's affinity for oxygen.

In the laboratory, automated blood cell counters rapidly provide accurate measurements of red cell content and cell indices. A stained blood smear provides information about the size, color, and shape of red cells and the presence of immature or abnormal cells. If blood smear results are abnormal, examination of the bone marrow may be important.

ANEMIA

Anemia is defined as an abnormally low hemoglobin level, number of circulating red blood cells, or both, resulting in diminished oxygen-carrying capacity of the blood. Anemia usually results from excessive loss (*i.e.,* bleeding) or destruction (*i.e.,* hemolysis) of red blood cells or from deficient red blood cell production because of a lack of nutritional elements or bone marrow failure.

Anemia is not a disease, but an indication of some disease process or alteration in body function. The manifestations of anemia can be grouped into three categories: (1) impaired oxygen transport and recruitment of compensatory mechanisms; (2) alterations in hemoglobin levels and red cell number and appearance; and (3) signs and symptoms associated with the pathologic process that is causing the anemia. The manifestations of anemia also depend on its severity, the rapidity of its development, and the affected person's age and health status. With rapid blood loss, circulatory shock and circulatory collapse may occur. Because the body adapts to slowly developing anemia, the amount of red cell mass lost may reach 50% without the occurrence of signs and symptoms.[1]

In anemia, the oxygen-carrying capacity of hemoglobin is reduced, causing tissue hypoxia. Tissue hypoxia can give rise

to fatigue, weakness, dyspnea, and sometimes angina. Brain hypoxia results in headache, faintness, and dim vision. The redistribution of the blood from cutaneous tissues or a lack of hemoglobin causes pallor of the skin, mucous membranes, conjunctiva, and nail beds. Tachycardia and palpitations may occur as the body tries to compensate with an increase in cardiac output. A flow-type systolic heart murmur may result from the turbulence caused by a decrease in blood viscosity. Ventricular hypertrophy and high-output heart failure may develop in persons with severe anemia, particularly those with pre-existing heart disease. Erythropoiesis is accelerated and may be recognized by diffuse bone pain and sternal tenderness. The production of 2,3-DPG is a compensatory mechanism that reduces the hemoglobin affinity for oxygen, as evidenced by a shift to the right in the oxygen–hemoglobin saturation curve; this causes more oxygen to be released to the tissues rather than remaining bound to hemoglobin.

Blood Loss Anemia

With anemia caused by bleeding, iron and other components of the erythrocyte are lost from the body. Blood loss may be acute or chronic.

Acute blood loss is accompanied by a loss of vascular volume and carries with it a risk of hypovolemia and shock (see Chapter 18). The red cells are normal in size and color. Hemodilution caused by movement of fluid into the vascular compartment produces a fall in red blood cell count, hemoglobin, and hematocrit. The hypoxia that results from blood loss stimulates red cell production by the bone marrow. If the bleeding is controlled and sufficient iron stores are available, the red cell concentration returns to normal within 3 to 4 weeks.

Chronic blood loss does not affect blood volume but instead leads to iron-deficiency anemia when iron stores are depleted. Because of compensatory mechanisms, patients commonly have no symptoms until the hemoglobin level is less than 8 g/dL. The red cells that are produced have too little hemoglobin, giving rise to microcytic hypochromic anemia.

Hemolytic Anemia

Hemolytic anemia is characterized by the (1) premature destruction of red cells, (2) retention in the body of iron and the other products of hemoglobin destruction, and (3) marked increase in erythropoiesis within the bone marrow.[2] Almost all types of hemolytic anemia are distinguished by normocytic and normochromic red cells. Because of the red blood cell's shortened life span, the bone marrow usually is hyperactive, resulting in an increase in the number of reticulocytes in the circulating blood. As with other types of anemias, the person experiences easy fatigability, dyspnea, and other signs and symptoms of impaired oxygen transport. The person may also have an increase in serum bilirubin and mild jaundice.

In hemolytic anemia, red cell breakdown can occur in the vascular compartment, or it can result from phagocytosis within the reticuloendothelial system. Intravascular hemolysis occurs as a result of complement fixation in transfusion reactions, mechanical injury, or toxic factors. It is characterized by hemoglobinemia and hemoglobinuria. Extravascular hemolysis occurs when abnormal red cells are phagocytized in the spleen. A common example is sickle cell anemia.

The cause of hemolytic anemia can be intrinsic or extrinsic to the red blood cell. Intrinsic causes include defects of the red cell membrane, the various hemoglobinopathies, and inherited enzyme defects. Acquired forms of hemolytic anemia are caused by agents extrinsic to the red blood cell, such as drugs, bacterial and other toxins, antibodies, and physical trauma. Although all these factors can cause premature and accelerated destruction of red cells, they cannot all be treated in the same way. Some respond to splenectomy, others respond to treatment with corticosteroid hormones, and still others do not resolve until the primary disorder is corrected.

Inherited Disorders of the Red Cell Membrane

Hereditary spherocytosis, transmitted as an autosomal dominant trait, is the most common inherited disorder of the red cell membrane. The disorder is a deficiency of membrane proteins (*i.e.*, spectrin and ankyrin) that leads to gradual loss of the membrane surface during the life span of the red blood cell, resulting in a tight sphere instead of a concave disk. Although the spherical cell retains its ability to transport oxygen, it is poorly deformable and susceptible to destruction as it passes through the venous sinuses of the splenic circulation. Clinical signs are variable but typically include mild anemia, splenomegaly, jaundice, and bilirubin gallstones. A life-threatening aplastic crisis may occur when a sudden disruption of red cell production (in most cases from a viral infection) causes a rapid drop in hematocrit and the hemoglobin level. The disorder usually is treated with splenectomy to reduce red cell destruction.

Hemoglobinopathies

Hemoglobinopathies represent abnormalities in hemoglobin structure that can lead to accelerated red cell destruction. Two main types of hemoglobinopathies can cause red cell hemolysis: the abnormal substitution of an amino acid in the hemoglobin molecule, as in sickle cell anemia, and the defective

synthesis of one of the polypeptide chains that form the globin portion of hemoglobin, as in the thalassemias.

Sickle Cell Disease (Anemia). Sickle cell disease is a chronic disorder resulting in organ failure and premature death. The disorder affects approximately 50,000 (0.1% to 0.2%) black Americans. Approximately 8% of black Americans carry the trait.[2]

Sickle cell disease results from a point mutation in the β chain of the hemoglobin molecule, with an abnormal substitution of a single amino acid, valine, for glutamic acid. Sickle hemoglobin (HbS) is transmitted by recessive inheritance and can manifest as sickle cell trait (*i.e.,* in heterozygotes with one HbS gene and one normal HbA gene) or sickle cell disease (*i.e.,* in homozygotes with two HbS genes). In the homozygote with sickle cell disease, almost all the hemoglobin is HbS. In the heterozygote with sickle cell trait, only approximately 40% of the hemoglobin is HbS.

In the homozygote, sickling occurs when the HbS becomes deoxygenated.[3] The deoxygenated hemoglobin aggregates and polymerizes, creating a semisolid gel that changes the shape and deformability of the cell (Fig. 13-6). Sickling of red cells is initially a reversible process with oxygenation. HbS returns to its normal depolymerized state. However, with repeated episodes of deoxygenation, the cells remain permanently sickled. These sickled red cells are abnormally adhesive, attach to the vessel wall, and cause accumulation of more cells that obstruct blood flow in the microcirculation, leading to tissue hypoxia.[3] Sickled cells have a rigid and nondeformable membrane, predisposing to premature destruction and hemolysis. Thus, the life span of the sickled cells is markedly reduced.

Perhaps the most important factor in promoting sickling is the amount of HbS and its interaction with other hemoglobin chains. The person with sickle cell trait who has less HbS has little tendency to sickle except during severe hypoxia and has virtually no symptoms. HbF does not interact with HbS or sickle; therefore, infants with sickle cell disease do not begin to experience the effects of the sickling until sometime

■ FIGURE 13-6 ■ Photograph of a sickled cell and a normal red blood cell. (© Dr. Gopal Murti, Science Photo Library, Science Source/Photo Researchers)

after 4 to 6 months of age, when the HbF has been replaced by HbS.

The factors associated with sickling and consequent blood vessel occlusion in persons with sickle cell disease include cold; stress; physical exertion; infection; illnesses that may cause hypoxia, acidosis, or dehydration; or even such trivial incidents as reduced oxygen tension induced by sleep. The rate of HbS polymerization is affected by the hemoglobin concentration in the cell. Thus dehydration, which increases the hemoglobin concentration, greatly facilitates sickling and vascular obstruction. Acidosis, or a fall in pH, which reduces the affinity of hemoglobin for oxygen, can increase sickling because it enhances the amount of deoxygenated HbS.

Persons with sickle cell disease experience problems associated with severe hemolytic anemia, chronic hyperbilirubinemia, and vaso-occlusion. Chronic hemolysis produces rather severe anemia, with hematocrit levels ranging from 18% to 30%.[2] The hyperbilirubinemia that results from the breakdown products of hemoglobin often leads to jaundice and the production of pigment stones in the gallbladder. Children with sickle cell disease may experience growth retardation and susceptibility to osteomyelitis.

Vaso-occlusion accounts for the most severe complications of sickle cell disease. An acute pain episode results from vessel occlusion and can affect almost any part of the body. Common sites obstructed by sickled cells include the abdomen, chest, bones, and joints. Multiple areas are frequently involved simultaneously, and symmetric involvement of both extremities is common. The frequency ranges from daily to yearly. Infarctions caused by sluggish blood flow can cause chronic damage to the liver, spleen, heart, kidneys, retina, and other organs. Acute chest syndrome is an atypical pneumonia resulting from pulmonary infarction. It affects approximately 40% of persons with sickle cell disease and is characterized by fever, chest pain, and cough.[4] The syndrome can cause chronic respiratory insufficiency and is a leading cause of death in sickle cell disease. The most serious complication is stroke resulting from cerebral occlusion. Stroke associated with vessel occlusion occurs in children 1 to 15 years of age and may recur in two thirds of those afflicted.

The spleen is especially susceptible to damage by sickle cell hemoglobin. Because of the spleen's sluggish blood flow and low oxygen tension, hemoglobin is deoxygenated and causes ischemia. Splenic injury begins as early as 3 to 6 months of age with intense congestion and is usually asymptomatic.[5] The congestion causes functional asplenia and predisposes the person to life-threatening infections by encapsulated organisms such as *Streptococcus pneumoniae, Haemophilus influenzae* type b, and *Klebsiella* species. Neonates and small children who have not had time to create antibodies to these organisms rely on the spleen for their removal.[5]

Most children with sickle cell disease are at risk for fulminant septicemia and death during the first 3 years of life, when bacteremia from encapsulated organisms occurs commonly even in normal children. Prophylactic penicillin should be begun as early as 2 months of age and continued until at least 5 years of age.[6] Maintaining full immunization, including administration of *H. influenzae* and hepatitis B vaccines, is recommended. The National Institutes of Health Committee on Management of Sickle Cell Disease also recommends administration of the 7-valent pneumococcal vaccine (see Chapter 20)

beginning at 2 to 6 months of age.[6] The 7-valent vaccine should be followed by immunization with the 23-valent pneumo-coccal vaccine at 24 months of age or after.[6]

There is no known cure for sickle cell anemia, so treatment to reduce symptoms includes pain control, hydration, and management of complications. Persons with the disorder need to avoid situations that precipitate sickling episodes, such as infections, cold exposure, severe physical exertion, acidosis, and dehydration. Infections are aggressively treated, and blood transfusions may be warranted in a crisis or given chronically in severe disease.

In the United States, screening programs have been implemented to detect newborns with sickle cell disease and other hemoglobinopathies so that appropriate interventions can be implemented. Hydroxyurea is a promising new treatment for the prevention of complications. The drug allows synthesis of more HbF and less HbS, thereby decreasing sickling.[4,6] Hematopoietic stem cell transplantation may offer the curative potential for sickle cell disease in the future.[6]

Thalassemias. In contrast to sickle cell anemia, the thalasse-mias result from absent or defective synthesis of the α or the β chains of hemoglobin. The β-thalassemias represent a defect in β-chain synthesis, and the α-thalassemias represent a defect in α-chain synthesis. The defect is inherited as a mendelian trait, and a person may be heterozygous for the trait and have a mild form of the disease or be homozygous and have the severe form of the disease. Like sickle cell anemia, the thalasse-mias occur with high degree of frequency in certain popu-lations. The β-thalassemias, sometimes called *Cooley's anemia* or *Mediterranean anemia,* are most common in the Mediterra-nean populations of southern Italy and Greece, and the α-thalassemias are most common among Asians. Both α- and β-thalassemias are common in Africans and black Americans.

Two factors contribute to the anemia that occurs in the thal-assemias: reduced hemoglobin synthesis and an imbalance in globin chain production. In α- and β-thalassemia, defective globin chain production leads to deficient hemoglobin pro-duction and the development of a hypochromic microcytic anemia. The unaffected type of chain continues to be synthe-sized, accumulates in the red cell, interferes with normal mat-uration, and contributes to red cell destruction and anemia. In the β-thalassemias, the excess α chains are denatured to form precipitates (*i.e.,* Heinz bodies) in the bone marrow red cell precursors.[2,7] These Heinz bodies impair DNA synthesis and cause damage to the red cell membrane. Severely affected red cell precursors are destroyed in the bone marrow, and those that escape intramedullary death are at increased risk of de-struction in the spleen.

The clinical manifestations of the β-thalassemias are based on the severity of the anemia. The presence of one normal gene in heterozygous persons (thalassemia minor) usually results in sufficient normal hemoglobin synthesis to prevent severe ane-mia.[2] Persons who are homozygous for the trait (thalassemia major) have severe, transfusion-dependent anemia evident at 6 to 9 months of age. Severe growth retardation affects children with the disorder. Increased hematopoiesis in response to erythropoietin causes bone marrow expansion, impairs bone growth, and causes bone abnormalities. The facial and cranial bones, in particular, tend to be enlarged and distorted.[2,8] In ad-dition, there is increased iron absorption, and splenomegaly

and hepatomegaly resulting from increased red cell destruc-tion.[2] Excess iron stores, which accumulate from increased di-etary absorption and repeated transfusions, can deposit in the myocardium, liver, and pancreas and produce organ injury. Cardiac disease resulting from iron overload and secondary hemochromatosis is a frequent cause of death. Frequent trans-fusions prevent most of the complications, and iron chelation therapy can reduce the iron overload and extend life into the fifth decade.[8] Bone marrow transplantation is a potential cure for some patients.

Synthesis of the α chains of the hemoglobin molecule is controlled by two pairs of genes; thus, α-thalassemia shows great variations in severity. Silent carriers who have deletion of a single α-thalassemia gene and those with deletion of two genes usually have no symptoms. The most severe form of α-thalassemia occurs in infants in whom all four α-thalassemia genes are deleted.[8,9] Such a defect results in a hemoglobin mol-ecule (Hb Bart's) that is formed exclusively from the chains of HbF. Hb Bart's, which has an extremely high oxygen affinity, cannot release oxygen in the tissues. Affected infants experience severe hypoxia and are stillborn or die shortly after birth unless intrauterine transfusions are given. Deletion of three of the four α-chain genes leads to unstable aggregates of β chains called *hemoglobin H* (HbH). The β chains are more soluble than the α chains, and their accumulation is less toxic to the red cells, so that senescent, rather than precursor, red cells are affected. Most persons with HbH have only mild to moderate hemolytic anemia, and manifestations of ineffective erythro-poiesis (*i.e.,* bone marrow expansion and iron overload) are absent.

Inherited Enzyme Defects

The most common inherited enzyme defect that results in he-molytic anemia is a deficiency of G6PD. The gene that deter-mines this enzyme is located on the X chromosome, and the defect is expressed only in males and homozygous females. There are many genetic variants of this disorder. The African variant has been found in 10% of black Americans.[2] The dis-order makes red cells more vulnerable to oxidants and causes direct oxidation of hemoglobin to methemoglobin and the de-naturing of the hemoglobin molecule to form Heinz bodies, which precipitate within the red blood cell. Hemolysis usually occurs as the damaged red blood cells move through the nar-row vessels of the spleen, causing hemoglobinemia, hemoglo-binuria, and jaundice. The hemolysis is short-lived, occurring 2 to 3 days after the trigger event. In blacks, the defect is mildly expressed and is not associated with chronic hemolytic anemia unless triggered by oxidant drugs, acidosis, or infection. The antimalarial drug primaquine, the sulfonamides, nitrofuran-toin, aspirin, phenacetin, some chemotherapeutics, and other drugs cause hemolysis. Free radicals generated by phagocytes during infections also are possible triggers.

Acquired Hemolytic Anemias

Several acquired factors exogenous to the red blood cell pro-duce hemolysis by direct membrane destruction or by antibody-mediated lysis. Various drugs, chemicals, toxins, venoms, and infections such as malaria destroy red cell membranes. Hemolysis can also be caused by mechanical factors such as prosthetic heart valves, vasculitis, and severe burns. Obstruc-tions in the microcirculation, as in disseminated intravascular

coagulation, thrombotic thrombocytopenic purpura, and renal disease, may traumatize the red cells by producing turbulence and changing pressure gradients.

Many hemolytic anemias are immune mediated, caused by antibodies that damage the red cell membrane. Autoantibodies may be produced by a person in response to drugs and disease. Alloantibodies come from an exogenous source and are responsible for transfusion reactions and hemolytic disease of the newborn.

The autoantibodies that cause red cell destruction are of two types: warm-reacting antibodies of the immunoglobulin G (IgG) type, which are maximally active at 37°C, and cold-reacting antibodies of the immunoglobulin M (IgM) type, which are optimally active at or near 4°C. The warm-reacting antibodies cause no morphologic or metabolic alteration in the red cell. Instead, they react with antigens on the red cell membrane, causing destructive changes that lead to spherocytosis, with subsequent phagocytic destruction in the spleen or reticuloendothelial system. They lack specificity for the ABO antigens but may react with the Rh antigens. The hemolytic reactions associated with the warm-reacting antibodies occur with an incidence of approximately 10 per 1 million. The reactions have a rapid onset, and persons usually have mild jaundice and manifestations of anemia. There are varied causes; approximately 50% are idiopathic, and 50% are drug induced or are related to cancers of the lymphoproliferative system (*e.g.*, chronic lymphocytic leukemia, lymphoma) or collagen diseases (*e.g.*, systemic lupus erythematosus).[2] The drug-related hemolytic anemias are usually benign conditions. The principle offenders are the antihypertensive drug α-methyldopa and the antiarrhythmic agent quinidine.[8]

The cold-reacting antibodies activate complement. Chronic hemolytic anemia caused by cold-reacting antibodies occurs with lymphoproliferative disorders and as an idiopathic disorder of unknown cause. The hemolytic process occurs in distal body parts, where the temperature may fall to less than 30°C. Vascular obstruction by red cells results in pallor, cyanosis of the body parts exposed to cold temperatures, and Raynaud's phenomenon (see Chapter 15). Hemolytic anemia caused by cold-reacting antibodies develops in only a few persons and is rarely severe.

The Coombs' test, or the antiglobulin test, is used to diagnose immune hemolytic anemias. It detects the presence of antibody or complement on the surface of the red cell.

Anemias of Deficient Red Cell Production

Anemia may result from the decreased production of erythrocytes by the bone marrow. A deficiency of nutrients for hemoglobin synthesis (iron) or DNA synthesis (cobalamin or folic acid) may reduce red cell production by the bone marrow. A deficiency of red cells also results when the marrow itself fails or is replaced by nonfunctional tissue.

Iron-Deficiency Anemia

Iron deficiency is a common worldwide cause of anemia affecting persons of all ages. The anemia results from dietary deficiency, loss of iron through bleeding, or increased demands. Because iron is a component of heme, a deficiency leads to decreased hemoglobin synthesis and consequent impairment of oxygen delivery.

Body iron is used repeatedly. When red cells become senescent and are broken down, their iron is released and reused in the production of new red cells. Despite this efficiency, small amounts of iron are lost in the feces and need to be replaced by dietary uptake. Iron balance is maintained by the absorption of 0.5 to 1.5 mg daily to replace the 1 mg lost in the feces. The average Western diet supplies this amount. The absorbed iron is more than sufficient to supply the needs of most individuals but may be barely adequate in women and young children. Dietary deficiency of iron is uncommon in developed countries, except in certain populations. Most iron is derived from meat, and when meat is not available, as for deprived populations, or is not a dietary constituent, as for vegetarians, iron deficiency may occur.

The usual reason for iron deficiency in adults is chronic blood loss because iron cannot be recycled to the pool. In men and postmenopausal women, blood loss may occur from gastrointestinal bleeding because of peptic ulcer, intestinal polyps, hemorrhoids, or cancer. Excessive aspirin intake may cause undetected gastrointestinal bleeding. In women, menstruation may account for an average of 1.5 mg of iron lost per day, causing a deficiency.[10] Although cessation of menstruation removes a major source of iron loss in the pregnant woman, iron requirements increase at this time and deficiency is common. The expansion of the mother's blood volume requires approximately 500 mg of additional iron, and the growing fetus requires approximately 360 mg during pregnancy. During the postnatal period, lactation requires approximately 1.0 mg of iron daily.[10]

A child's growth places extra demands on the body. Blood volume increases, with a greater need for iron. Iron requirements are proportionally higher in infancy (3 to 24 months) than at any other age, although they are also increased in childhood and adolescence. In infancy, the two main causes of iron-deficiency anemia are low iron levels at birth because of maternal deficiency and a diet consisting mainly of cow's milk, which is low in absorbable iron. Adolescents are also susceptible to iron deficiency because of high requirements due to growth spurts, dietary deficiencies, and menstrual loss.[11]

Iron deficiency anemia is characterized by low hemoglobin and hematocrit values, decreased iron stores, and low serum iron and ferritin levels. The red cells are decreased in number and are microcytic and hypochromic. Poikilocytosis (irregular shape) and anisocytosis (irregular size) are also present (Fig 13-7). The laboratory values indicate reduced MCHC and MCV. Membrane changes may predispose to hemolysis, causing further loss of red cells.

The manifestations of iron-deficiency anemia are related to lack of hemoglobin and impaired oxygen transport. Depending on the severity of the anemia, fatigability, palpitations, dyspnea, angina, and tachycardia may occur. Epithelial tissue atrophy is common and results in waxy pallor, brittle hair and nails, smooth tongue, sores in the corners of the mouth, and sometimes dysphagia and decreased acid secretion. A poorly understood symptom that sometimes is seen is pica, the bizarre compulsive eating of ice, dirt, or other abnormal substances.

The treatment of iron-deficiency anemia is directed toward controlling chronic blood loss, increasing dietary intake of iron, and administering supplemental iron. Ferrous sulfate, which is the usual oral replacement therapy, replenishes iron stores in several months. Parenteral iron (iron dextran) therapy
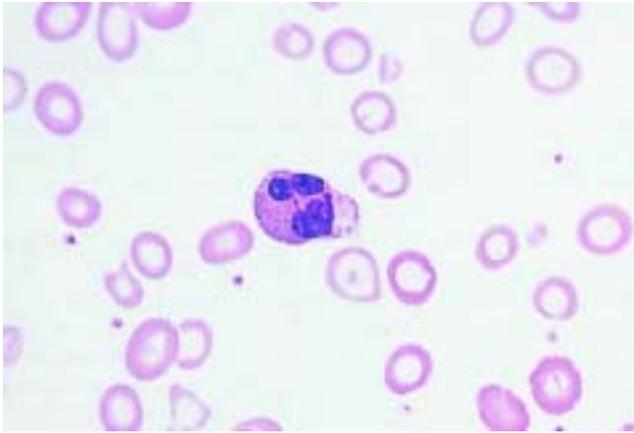
■ FIGURE 13-7 ■ Iron deficiency anemia. A peripheral smear shows hypochromic and microcytic erythrocytes. Poikilocytosis (irregular shape) and anisocytosis (irregular size) are often observed. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1077]. Philadelphia: Lippincott-Raven)
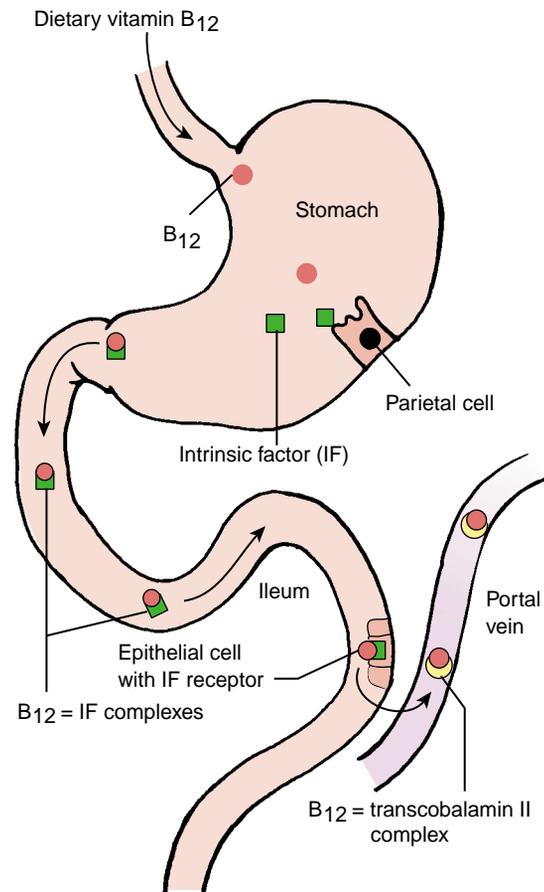

■ FIGURE 13-8 ■ Absorption of vitamin B_{12}.

may be used when oral forms are not tolerated or are ineffective. Caution is required because of the possibility of severe hypersensitivity reactions.

Megaloblastic Anemias

Megaloblastic anemias are caused by abnormal nucleic acid synthesis that results in enlarged red cells (MCV >100 fL) and deficient nuclear maturation. Cobalamin (vitamin B_{12}) and folic acid deficiencies are the most common cause of megaloblastic anemias. Because megaloblastic anemias develop slowly, there are often few symptoms until the anemia is far advanced.

Cobalamin (Vitamin B_{12})-Deficiency Anemia. Vitamin B_{12} serves as a cofactor for two important reactions in humans. It is essential for the synthesis of DNA. When it is deficient, nuclear maturation and cell division, especially of the rapidly proliferating red cells, fail to occur. It is also involved in a reaction that prevents abnormal fatty acids from being incorporated into neuronal lipids. This abnormality may predispose to myelin breakdown and production of the neurologic complications of vitamin B_{12} deficiency.

Vitamin B_{12} is found in all foods of animal origin. Dietary deficiency is rare and usually found only in strict vegetarians who avoid all dairy products as well as meat and fish. It is absorbed by a unique process. After release from the animal protein, vitamin B_{12} is bound to intrinsic factor, a protein secreted by the gastric parietal cells (Fig. 13-8). The vitamin B_{12}-intrinsic factor complex travels to the ileum, where membrane receptors allow the binding of the complex and transport of B_{12} across the membrane. From there it is bound to its carrier protein, transcobalamin II, which carries vitamin B_{12} in the circulation to its storage and tissue sites. Any defects in this pathway may cause a deficiency. An important cause of vitamin B_{12} deficiency is pernicious anemia, resulting from a hereditary atrophic gastritis. As discussed in Chapter 27, immune-mediated chronic atrophic gastritis is a disorder that destroys the gastric mucosa, with loss of parietal cells and production of

antibodies that interfere with the binding of vitamin B_{12} to the intrinsic factor. Other causes of vitamin B_{12} deficiency anemia include gastrectomy, ileal resection, and malabsorption syndromes in which vitamin B_{12} and other vitamin B compounds are poorly absorbed.

The hallmark of vitamin B_{12} deficiency is megaloblastic anemia. When vitamin B_{12} is deficient, the red cells that are produced are abnormally large because of excess ribonucleic acid production of hemoglobin and structural protein (Fig. 13-9). They have flimsy membranes and are oval, rather than biconcave. These oddly shaped cells have a short life span that can be measured in weeks, rather than months. The MCV is elevated, and the MCHC is normal.

Neurologic changes that accompany the disorder are caused by deranged methylation of myelin protein. Demyelination of the dorsal and lateral columns of the spinal cord causes symmetric paresthesias of the feet and fingers, loss of vibratory and position sense, and eventual spastic ataxia. In more advanced cases, cerebral function may be altered. In some cases, dementia and other neuropsychiatric changes may precede hematologic changes.

Diagnosis of vitamin B_{12} deficiency is made by finding an abnormally low vitamin B_{12} serum level. The Schilling test, which measures the 24-hour urinary excretion of radiolabeled vitamin B_{12} administered orally, is used to document decreased absorption of vitamin B_{12}. Lifelong treatment consisting of
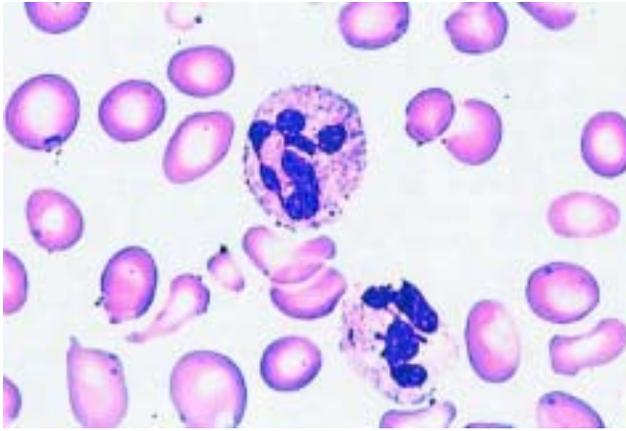
■ **FIGURE 13-9** ■ Peripheral blood smear of patient with vitamin B$_{12}$ deficiency (pernicious anemia) that shows prominent megablastic anemia. The erythrocytes are large, often with oval shape, and are associated with poikilocytosis and teardrop shapes. The neutrophils are hypersegmented. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 1076]. Philadelphia: Lippincott-Raven)

intramuscular injections of vitamin B$_{12}$ reverses the anemia and improves the neurologic status.

Folic Acid-Deficiency Anemia. Folic acid is also required for DNA synthesis and red cell maturation, and its deficiency produces the same type of red cell changes that occur in vitamin B$_{12}$ deficiency anemia (*i.e.,* increased MCV and normal MCHC). Symptoms are also similar, but the neurologic manifestations are not present.

Folic acid is readily absorbed from the intestine. It is found in vegetables (particularly the green leafy types), fruits, cereals, and meats. However, much of the vitamin is lost in cooking. The most common causes of folic acid deficiency are malnutrition or dietary lack, especially in the elderly or in association with alcoholism, and malabsorption syndromes such as sprue or other intestinal disorders. In neoplastic disease, tumor cells compete for folate, and deficiency is common. Some drugs used to treat seizure disorders (*e.g.,* primidone, phenytoin, phenobarbital) and triamterene, a diuretic, predispose to a deficiency by interfering with folic acid absorption. Methotrexate, a folic acid analog used in the treatment of cancer, impairs the action of folic acid by blocking its conversion to the active form.

Because pregnancy increases the need for folic acid 5- to 10-fold, a deficiency commonly occurs. Poor dietary habits, anorexia, and nausea are other reasons for folic acid deficiency during pregnancy. Studies also show an association between folate deficiency and neural tube defects.[12] The Public Health Service recommends that all women of childbearing age should take 400 micrograms (μg) of folic acid daily. It is estimated that as many as 50% of neural tube defects could be prevented.[12] The Institute of Medicine Panel on Folate and Other B Vitamins and Choline recently revised the recommended daily allowance (RDA) for pregnant women to 600 μg.[13] To ensure adequate folate consumption, the U.S. Food and Drug Administration has issued a recommendation for the addition of folate to cereal grain products.[14]

Aplastic Anemia

Aplastic anemia (*i.e.,* bone marrow depression) describes a primary condition of bone marrow stem cells that results in a reduction of all three hematopoietic cell lines—red blood cells, white blood cells, and platelets—with fatty replacement of bone marrow. Pure red cell aplasia, in which only the red cells are affected, rarely occurs.

Anemia results from the failure of the marrow to replace senescent red cells that are destroyed and leave the circulation, although the cells that remain are of normal size and color. At the same time, because the leukocytes, particularly the neutrophils, and the thrombocytes have a short life span, a deficiency of these cells usually is apparent before the anemia becomes severe.

The onset of aplastic anemia may be insidious, or it may strike with suddenness and great severity. It can occur at any age. The initial presenting symptoms include weakness, fatigability, and pallor caused by anemia. Petechiae (*i.e.,* small, punctate skin hemorrhages) and ecchymoses (*i.e.,* bruises) often occur on the skin, and bleeding from the nose, gums, vagina, or gastrointestinal tract may occur because of decreased platelet levels. The decrease in the number of neutrophils increases susceptibility to infection.

Among the causes of aplastic anemia are exposure to high doses of radiation, chemicals, and toxins that suppress hematopoiesis directly, or through immune mechanisms. Chemotherapy and irradiation commonly result in bone marrow depression. Identified toxic agents include benzene, the antibiotic chloramphenicol, and the alkylating agents and antimetabolites used in the treatment of cancer (see Chapter 5). Aplastic anemia caused by exposure to chemical agents may be an idiosyncratic reaction because it affects only certain susceptible persons. It typically occurs weeks after use of a drug is initiated. Such reactions often are severe and sometimes irreversible and fatal. Aplastic anemia can develop in the course of many infections and has been reported most often as a complication of viral hepatitis, mononucleosis, and other viral illnesses, including acquired immunodeficiency syndrome (AIDS). In two thirds of cases, the cause is unknown, and these are called *idiopathic aplastic anemia.*

Therapy for aplastic anemia in the young and severely affected includes stem cell replacement by bone marrow or peripheral blood transplantation. For those who are not transplantation candidates, immunosuppressive therapy with lymphocyte immune globulin (*i.e.,* antithymocyte globulin) prevents suppression of proliferating stem cells, producing remission in as many as 50% of patients.[15] Patients with aplastic anemia should avoid the offending agents and be treated with antibiotics for infection. Red cell transfusions to correct the anemia and platelets and corticosteroid therapy to minimize bleeding may also be required.

Chronic Disease Anemias

Anemia often occurs as a complication of chronic infections, inflammation, and cancer. Chronic diseases commonly associated with anemia include AIDS, osteomyelitis, rheumatoid arthritis, and Hodgkin's disease. It is theorized that the short life span, deficient red cell production, and low serum iron are caused by actions of macrophages and lymphocytes in response to cell injury. Macrophages sequester iron in the spleen and contribute to red cell destruction, and the lymphocytes re-

lease cytokines that suppress erythropoietin production and action.[16] The mild to moderate anemia is usually reversed when the underlying disease is treated.

Chronic renal failure almost always results in a normocytic, normochromic anemia, primarily because of a deficiency of erythropoietin. Uremic toxins also interfere with the actions of erythropoietin and red cell production. They also cause hemolysis and bleeding tendencies, which contribute to the anemia. Until recently, dialysis and red cell transfusions constituted the only therapy. Recombinant erythropoietin injected several times each week for 10 or more weeks dramatically elevates the hemoglobin level and hematocrit to a range of 32% to 38% and eliminates the need for transfusions.[17] Oral iron is usually required for a good response.

> **In summary,** anemia is a condition of an abnormally low hemoglobin level, number of circulating red blood cells, or both. Anemia can result from excessive blood loss, red cell destruction caused by hemolysis, or deficient hemoglobin or red cell production. Blood loss anemia can be acute or chronic. With bleeding, iron and other components of the erythrocyte are lost from the body. Hemolytic anemia is characterized by the premature destruction of red cells, with retention in the body of iron and the other products of red cell destruction. Hemolytic anemia can be caused by defects in the red cell membrane, hemoglobinopathies (sickle cell anemia or thalassemia), or inherited enzyme defects (G6PD deficiency). Acquired forms of hemolytic anemia are caused by agents extrinsic to the red blood cell, such as drugs, bacterial and other toxins, antibodies, and physical trauma. Iron-deficiency anemia, which is characterized by decreased hemoglobin synthesis, can result from dietary deficiency, loss of iron through bleeding, or increased demands for red cell production. Vitamin B_{12} and folic acid deficiency impair red cell production by interfering with DNA synthesis. Aplastic anemia is caused by bone marrow suppression and usually results in a reduction of white blood cells and platelets, as well as red blood cells.
>
> The manifestations of anemia include those associated with impaired oxygen transport, recruitment of compensatory mechanisms, and the underlying process causing the anemia.

POLYCYTHEMIA

Polycythemia is an abnormally high total red blood cell mass with a hematocrit greater than 54% in males and 51% in females.[18] It is categorized as relative, primary, or secondary. In relative polycythemia, the hematocrit rises because of a loss of plasma volume without a corresponding decrease in red cells. This may occur with water deprivation, excess use of diuretics, or gastrointestinal losses. Relative polycythemia is corrected by increasing the vascular fluid volume.

Primary polycythemia, or polycythemia vera, is a proliferative disease of the pluripotent cells of the bone marrow characterized by an absolute increase in total red blood cell mass accompanied by elevated white cell and platelet counts. It most

commonly is seen in men between the ages of 40 and 60 years. In polycythemia vera, the manifestations are related to an increase in the red cell count, hemoglobin level, and hematocrit with increased blood volume and viscosity. Commonly reported symptoms include headache, dizziness, and some difficulty with hearing and vision because of decreased cerebral blood flow. Hypertension is common, the result of an increase in blood viscosity. Venous stasis gives rise to a plethoric appearance or dusky redness—even cyanosis—particularly of the lips, fingernails, and mucous membranes. Because of the increased concentration of blood cells, the person may experience itching and pain in the fingers or toes, and the hypermetabolism may induce night sweats and weight loss. Thrombosis, caused by increased blood viscosity and stagnation of blood flow, is a common complication of polycythemia vera and the major cause of morbidity and mortality.[18]

The goal of treatment in primary polycythemia is to reduce blood viscosity. This can be done by withdrawing blood by means of periodic phlebotomy to reduce red cell volume. Control of platelet and white cell counts is accomplished by suppressing bone marrow function with chemotherapy or radiation therapy.

Secondary polycythemia results from a physiologic increase in the level of erythropoietin, commonly as a compensatory response to hypoxia. The causes of secondary polycythemia due to hypoxia include living at high altitudes, chronic heart and lung disease, and smoking. Treatment of secondary polycythemia focuses on relieving hypoxia. For example, continuous low-flow oxygen therapy can be used to correct the severe hypoxia that occurs in some persons with chronic obstructive lung disease.

> **In summary,** polycythemia describes a condition in which the red blood cell mass is increased. It can present as a relative, primary, or secondary disorder. Relative polycythemia results from a loss of vascular fluid and is corrected by replacing the fluid. Primary polycythemia, or polycythemia vera, is a proliferative disease of the bone marrow with an absolute increase in total red blood cell mass accompanied by elevated white cell and platelet counts. Secondary polycythemia results from increased erythropoietin levels caused by hypoxic conditions such as chronic heart and lung disease. Many of the manifestations of polycythemia are related to increased blood volume and viscosity that lead to hypertension and stagnation of blood flow.

AGE-RELATED CHANGES IN RED BLOOD CELLS

Red Cell Changes in the Neonate

At birth, changes in the red blood cell indices reflect the transition to extrauterine life and the need to transport oxygen from the lungs (Table 13-2). Hemoglobin concentrations at birth are high, reflecting the high synthetic activity in utero to provide adequate oxygen delivery.[19] Toward the end of the first postnatal week, the hemoglobin concentration begins to decline, gradually falling to a minimum value at approximately age

TABLE 13-2	Red Cell Values for Term Infants			
Age	RBC × 10⁶/mL Mean ± SD	Hb (g/dL) Mean ± SD	Hct (%) Mean ± SD	MCV (fL) Mean ± SD
Days				
1	5.14 ± 0.7	19.3 ± 2.2	61 ± 7.4	119 ± 9.4
4	5.00 ± 0.6	18.6 ± 2.1	57 ± 8.1	114 ± 7.5
7	4.86 ± 0.6	17.9 ± 2.5	56 ± 9.4	118 ± 11.2
Weeks				
1–2	4.80 ± 0.8	17.3 ± 2.3	54 ± 8.3	112 ± 19.0
3–4	4.00 ± 0.6	14.2 ± 2.1	43 ± 5.7	105 ± 7.5
8–9	3.40 ± 0.5	10.7 ± 0.9	31 ± 2.5	93 ± 12.0
11–12	3.70 ± 0.3	11.3 ± 0.9	33 ± 3.3	88 ± 7.9

Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume.
(Adapted from Matoth Y., Zaizor R., Varsano I. [1971]. Postnatal changes in some red cell parameters. *Acta Paediatrica Scandinavica 60*, 317)

2 months. The red cell count, hematocrit, and MCV likewise fall. The factors responsible for the decline include reduced red cell production and plasma dilution caused by increased blood volume with growth. Neonatal red cells also have a shorter life span of 50 to 70 days and are thought to be more fragile than those of older persons. During the early neonatal period, there is also a switch from HbF to HbA. The amount of HbF in term infants varies from 53% to 95% of the total hemoglobin and decreases by approximately 3% per week after birth.[20] In an infant 6 months of age, HbF usually accounts for less than 2% of total hemoglobin. The switch to HbA provides greater unloading of oxygen to the tissues because HbA has a lower affinity for oxygen than does HbF. Infants who are small for gestational age, those born to mothers who have diabetes or smoke, and those who experienced hypoxia in utero have higher total hemoglobin levels, higher HbF levels, and a delayed switch to HbA.

A physiologic anemia of the newborn develops at approximately 2 months of age. It seldom produces symptoms and cannot be altered by nutritional supplements. Anemia of prematurity, an exaggerated physiologic response in low–birth-weight infants, is thought to result from a poor erythropoietin response. The hemoglobin level rapidly declines after birth to a low of 7 to 10 g/dL at approximately 6 weeks of age. Signs and symptoms include apnea, poor weight gain, pallor, decreased activity, and tachycardia. In infants born before 33 weeks' gestation or those with hematocrits of less than 33%, the clinical features are more evident. One study suggests that the protein content of breast milk may not be sufficient for hematopoiesis in the premature infant. Protein supplementation significantly increases the hemoglobin concentrations between the ages of 4 and 10 weeks.[19]

Anemia at birth, characterized by pallor, congestive heart failure, or shock, usually is caused by hemolytic disease of the newborn. Bleeding from the umbilical cord, internal hemorrhage, congenital hemolytic disease, or frequent blood sampling are other possible causes of anemia. The severity of symptoms and presence of coexisting disease may warrant red cell transfusion.

Hyperbilirubinemia in the Neonate

Hyperbilirubinemia, an increased level of serum bilirubin, is a common cause of jaundice in the neonate. A benign, self-limited condition, it most often is related to the developmental state of the neonate. Rarely, cases of hyperbilirubinemia are pathologic and may lead to kernicterus and serious brain damage.

In the first week of life, approximately 60% of term and 80% of preterm neonates have jaundice.[21] This physiologic jaundice appears in term infants on the second or third day of life. Under normal circumstances, the indirect bilirubin in umbilical cord blood is 1 to 3 mg/dL and rises at a rate of less than 5 mg/dL/24 hours, peaking at 5 to 6 mg/dL between the second and fourth days and decreasing to less than 2 mg/dL between the fifth and seventh days of life.[21] The increase in bilirubin is related to the increased red cell breakdown and the inability of the immature liver to conjugate bilirubin. Premature infants exhibit a similar but slower rise in serum bilirubin level, perhaps because of poor hepatic uptake and reduced albumin binding of bilirubin. This generally results in higher bilirubin levels, with peak levels of 8 to 12 mg/dL being reached on the fifth to seventh day. Most neonatal jaundice resolves within 1 week and is untreated.

A search to determine the cause of the jaundice is usually made when (1) the jaundice appears during the first 24 to 36 hours of life or persists beyond 10 to 14 days, (2) serum bilirubin rises at a rate greater than 5 mg/dL/24 hours, (3) serum bilirubin is greater than 12 mg/dL in a full term infant or 10 to 14 mg/dL in preterm infants, (4) or the direct-reacting bilirubin is greater than 2 mg/dL at any time.

Many factors cause elevated bilirubin levels in the neonate: breast-feeding, hemolytic disease of the newborn, hypoxia, infections, and acidosis. Bowel or biliary obstruction and liver disease are less common causes. Associated risk factors include prematurity, Asian ancestry, and maternal diabetes. Breast milk jaundice occurs in approximately 2% of breast-fed infants.[21] These neonates accumulate significant levels of unconjugated bilirubin 7 days after birth that reach maximum levels during the third week of life. It is thought that the breast

milk contains fatty acids that inhibit bilirubin conjugation in the neonatal liver. A factor in breast milk is also thought to increase the absorption of bilirubin in the duodenum. This type of jaundice disappears if breast-feeding is discontinued. Breast-feeding can be resumed in 3 to 4 days without any hyperbilirubinemia ensuing.

Hyperbilirubinemia places the neonate at risk for the development of a neurologic syndrome called *kernicterus.* This condition is caused by the accumulation of unconjugated bilirubin in brain cells. Unconjugated bilirubin is lipid soluble, crosses the permeable blood-brain barrier of the neonate, and is deposited in cells of the basal ganglia, causing brain damage. The precise blood level of unconjugated bilirubin or duration of exposure necessary to produce toxic effects is largely unknown. The less mature the infant, the greater the susceptibility to kernicterus. Asphyxia and hyperosmolality may damage the blood-brain barrier and increase the risk of brain damage.[21]

Symptoms may appear 2 to 5 days after birth in term infants and as late as 7 days in premature infants. Lethargy, poor feeding, and short-term behavioral changes may be evident in mildly affected infants. Severe manifestations include rigidity, tremors, ataxia, and hearing loss. Extreme cases cause seizures and death. Most survivors of severe hyperbilirubinemia are seriously damaged and by 3 years of age exhibit involuntary muscle spasm, seizures, mental retardation, and deafness.

Hyperbilirubinemia in the neonate is treated with phototherapy or exchange transfusion. Phototherapy is more commonly used to treat infants with jaundice and reduce the risk of kernicterus. Exposure to fluorescent light in the blue range of the visible spectrum (420- to 470-nm wavelength) reduces bilirubin levels. Bilirubin in the skin absorbs the light energy and is converted to a structural isomer that is more water soluble and can be excreted in the stool and urine. Exchange transfusion is considered when signs of kernicterus are evident or hyperbilirubinemia is sustained or rising and unresponsive to phototherapy.

Hemolytic Disease of the Newborn

Erythroblastosis fetalis, or hemolytic disease of the newborn, occurs in Rh-positive infants of Rh-negative mothers who have been sensitized. The mother can produce anti-Rh antibodies from pregnancies in which the infants are Rh positive or by blood transfusions of Rh-positive blood. The Rh-negative mother usually becomes sensitized during the first few days after delivery, when fetal Rh-positive red cells from the placental site are released into the maternal circulation. Because the antibodies take several weeks to develop, the first Rh-positive infant of an Rh-negative mother usually is not affected. Infants with Rh-negative blood have no antigens on their red cells to react with the maternal antibodies and are not affected.

After an Rh-negative mother has been sensitized, the Rh antibodies from her blood are transferred to subsequent infants through the placental circulation. These antibodies react with the red cell antigens of the Rh-positive infant, causing agglutination and hemolysis. This leads to severe anemia with compensatory hyperplasia and enlargement of the blood-forming organs, including the spleen and liver, in the fetus. Liver function may be impaired, with decreased production of albumin causing massive edema, called *hydrops fetalis.* If blood

levels of unconjugated bilirubin are abnormally high because of red cell hemolysis, there is danger of kernicterus developing in the infant, resulting in severe brain damage or death.

Several advances have served to significantly decrease the threat to infants born to Rh-negative mothers: prevention of sensitization, antenatal identification of the at-risk fetus, and intrauterine transfusion to the affected fetus. The injection of Rh immune globulin (*i.e.*, gamma-globulin–containing Rh antibody) prevents sensitization in Rh-negative mothers who have given birth to Rh-positive infants if administered at 28 weeks' gestation and within 72 hours of delivery, abortion, genetic amniocentesis, or fetal-maternal bleeding. After sensitization has developed, the immune globulin is of no value. Since 1968, the year Rh immune globulin was introduced, the incidence of sensitization of Rh-negative women has dropped dramatically. Early prenatal care and screening of maternal blood continue to be important in reducing immunization. Efforts to improve therapy are aimed at production of monoclonal anti-D, the Rh antibody.

In the past, approximately 20% of erythroblastotic fetuses died in utero. Fetal Rh phenotyping can now be performed to identify at-risk fetuses during the first trimester using fetal blood or amniotic cells.[22] Hemolysis in these fetuses can be treated by intrauterine transfusions of red cells through the umbilical cord. Exchange transfusions are administered after birth by removing and replacing the infant's blood volume with type O Rh-negative blood. The exchange transfusion removes most of the hemolyzed red cells and some of the total bilirubin, treating the anemia and hyperbilirubinemia.

Red Cell Changes With Aging

Aging is associated with red cell changes. Bone marrow cellularity declines with age, from approximately 50% cellularity at age 65 years to approximately 30% at age 75 years. The decline may reflect osteoporosis, rather than a decrease in hematopoietic cells.[23]

Hemoglobin levels decline after middle age. In studies of men older than 60 years of age, mean hemoglobin levels ranged from 15.3 to 12.4 g/dL, with the lowest levels found in the oldest persons. The decline is less in women, with mean levels ranging from 13.8 to 11.7 mg/dL.[23] In most elderly persons with no symptoms, lower hemoglobin levels result from iron deficiency and anemia of chronic disease. Orally administered iron is poorly used in older adults, despite normal iron absorption. Underlying neoplasms also may contribute to anemia in this population.

In summary, hemoglobin concentrations at birth are high, reflecting the in utero need for oxygen delivery; toward the end of the first postnatal week, these levels begin to decline, gradually falling to a minimum value at approximately 2 months of age. During the early neonatal period, there is a shift from fetal to adult hemoglobin. Many infants have physiologic jaundice because of hyperbilirubinemia during the first week of life, probably related to increased red cell breakdown and the inability of the infant's liver to conjugate bilirubin. The term *kernicterus* describes elevated levels of lipid-soluble, unconjugated bilirubin, which can be toxic to brain cells.

Depending on severity, the condition is treated with phototherapy or exchange transfusions (or both). Hemolytic disease of the newborn occurs in Rh-positive infants of Rh-negative mothers who have been sensitized. It involves hemolysis of infant red cells in response to maternal Rh antibodies that have crossed the placenta. Administration of Rh immune globulin to the mother within 72 hours of delivery of an Rh-positive infant, abortion, or amniocentesis prevents sensitization.

Aging is associated with red cell changes. Bone marrow cellularity decreases, and there is a decrease in hemoglobin.

REVIEW QUESTIONS

■ Relate the function of the red blood cell to the manifestations of anemia.

■ Explain why the appearance of an increased number of reticulocytes in the blood is suggestive of blood loss and why a low ferritin level suggests the need for iron replacement therapy.

■ Explain why infants with sickle cell anemia usually do not display evidence of the disease until their hemoglobin F has been replaced with hemoglobin A.

■ Explain why fever, extreme exercise, and going to high altitudes produce sickling in persons with sickle cell anemia.

■ What is the common reason for the development of iron-deficiency anemia in infancy, adolescence, and in pregnant women?

■ Describe the relation between vitamin B_{12} deficiency and megaloblastic anemia. Explain why a person with sickle cell anemia who takes folic acid may not show evidence of megaloblastic anemia on laboratory tests but may have progressive neurologic changes caused by vitamin B_{12} deficiency.

■ Explain why ecchymosis, signs of platelet deficiency, and decreased resistance to infection occur before signs of a decreased red blood cell count in persons with aplastic anemia.

■ Explain the pathogenesis of secondary polycythemia in persons with chronic lung disease.

■ Describe the pathogenesis of hemolytic disease of the newborn and compare the difference between conjugated and unconjugated bilirubin in terms of causing neurologic damage.

connection—●

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