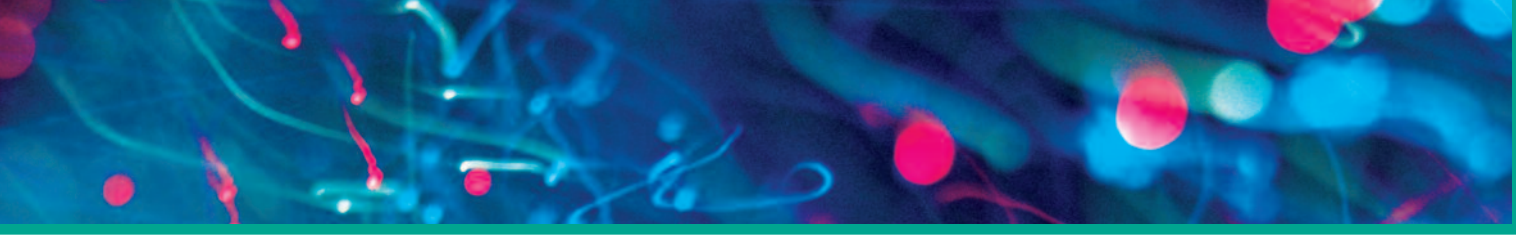

Chapter 11

The Red Blood Cell and Alterations in Oxygen Transport

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 20, 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 erythrocytes or mature red blood cells are the most common type of blood cell, being 500 to 1000 times more numerous than other blood cells. The erythrocyte is a nonnucleated, thin, biconcave disk (Fig. 11-1). This unique shape contributes in two ways to the oxygen (O_2) transport function of the erythrocyte. The biconcave shape provides a larger surface area for O_2 diffusion than would a spherical cell of the same volume, and the thinness of the cell membrane enables O_2 to diffuse rapidly between the exterior and innermost regions of the cell. Another structural feature that facilitates the transport function of the red blood cell is the flexibility of its membrane. The biconcave shape and flexibility of the red cell membrane are maintained by a network of fibrous proteins, especially one called *spectrin*, attached to the cytoplasmic side of the cell membrane. This complex arrangement allows for the inherent deformability of red cells as they squeeze through capillaries one-third their diameter without rupturing.

The most important anatomic feature that enables the red blood cell to transport O_2 is the hemoglobin it contains. Because O_2 is poorly soluble in plasma, about 95% to 98% is carried bound to hemoglobin. The hemoglobin molecule is composed of two pairs of structurally different alpha (α)

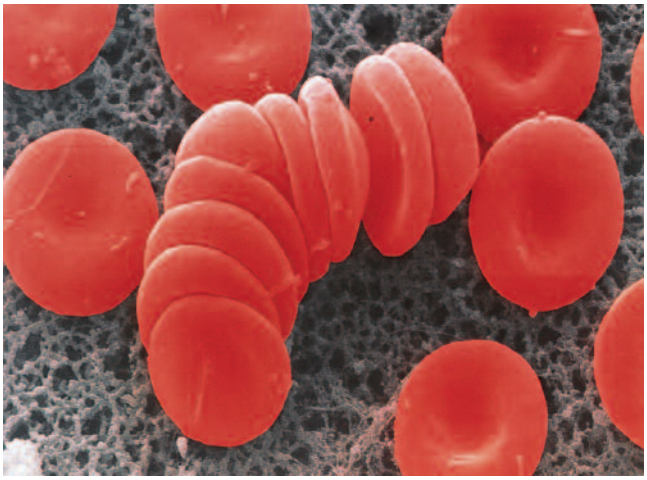

FIGURE 11-1 Scanning electron micrograph of normal red blood cells showing their normal concave appearance (×3000). (© Andrew Syred, Science Photo Lab, Science Source/Photo Researchers.)

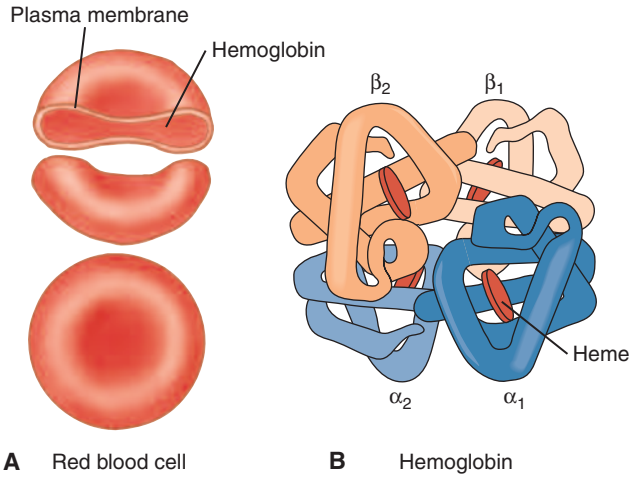

FIGURE 11-2 (**A**) Biconcave structure of the red blood cell as shown in cross-sectional side view and in lateral surface view. (**B**) Hemoglobin molecule, showing the four iron-containing heme subunits.

and beta (β) polypeptide chains (Fig. 11-2). Each of the four polypeptide chains consists of a globin (protein) portion and heme unit, which surrounds an atom of iron that binds oxygen.[1] Thus, each molecule of hemoglobin can carry four molecules of oxygen. Hemoglobin is a natural pigment; because of its iron content, it appears reddish when oxygen is attached and has a bluish cast when deoxygenated.

There are two major types of normal hemoglobin—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 gamma (γ) chains substituted for the α chains. Because of this chain substitution, HbF has a high affinity for oxygen. This affinity facilitates the transfer of oxygen across the placenta from the HbA in the mother's blood to the HbF in the fetus's blood. HbF is replaced within 6 months of birth by HbA.

KEY CONCEPTS

Red Blood Cells

- The function of red blood cells, facilitated by the iron-containing hemoglobin molecule, is to transport oxygen from the lungs to the tissues.
- The production of red blood cells, which is regulated by erythropoietin, occurs in the bone marrow and requires iron, vitamin B_{12}, and folate.
- The red blood cell, which has a life span of approximately 120 days, is broken down in the spleen; the degradation products such as iron and amino acids are recycled.
- The heme molecule, which is released from the red blood cell during the degradation process, is converted to bilirubin and transported to the liver, where it is removed and rendered water soluble for elimination in the bile.

HEMOGLOBIN SYNTHESIS

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 2 g in women and up to 6 g in men.[2] Body iron is found in several compartments. About 80% is complexed to heme in hemoglobin, and most of the remaining iron (about 20%) is stored in the bone marrow, liver, spleen, and other organs. Iron in the hemoglobin compartment is recycled. When red blood cells age and are destroyed in the spleen, the iron from their hemoglobin is released into the circulation and returned to the bone marrow for incorporation into new red blood 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. 11-3). When body stores of iron are diminished or erythropoiesis is stimulated, absorption is increased. Normally, some iron is sequestered in the intestinal epithelial cells and is lost in the feces as these cells slough off. The iron that is absorbed enters the circulation, where it attaches a transport protein called *transferrin*. From the circulation, iron can be deposited in tissues such as the liver, where it is stored as *ferritin*, a protein–iron complex, which can easily return to the circulation. Serum ferritin levels, which can be

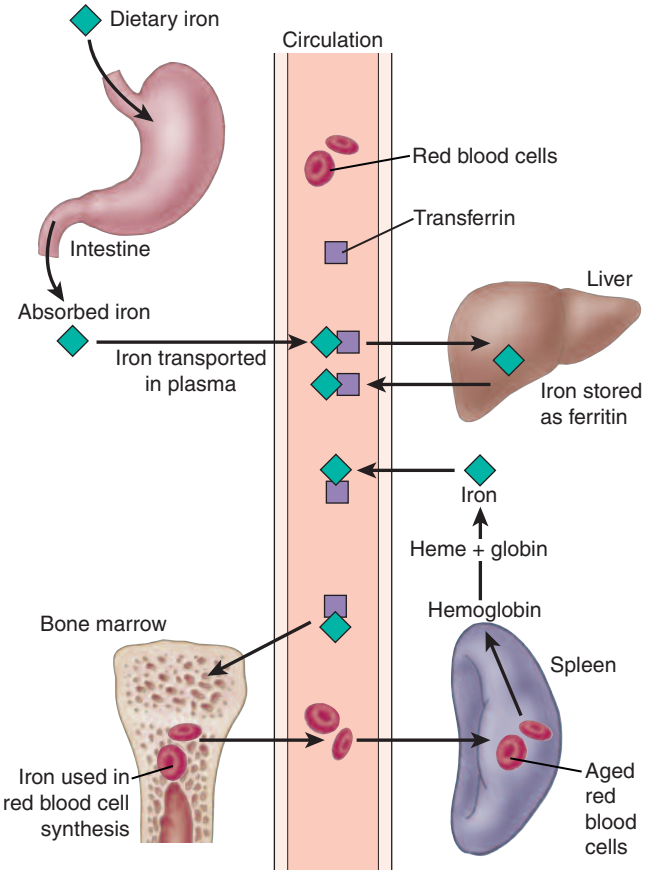

FIGURE 11-3 Diagrammatic representation of the iron cycle, including its absorption from the gastrointestinal tract, transport in the circulation, storage in the liver, recycling from aged red cells destroyed in the spleen, and use in the bone marrow synthesis of red blood cells.

measured in the laboratory, provide an index of body iron stores.

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 blood cells are derived from precursor cells called *erythroblasts,* which are continuously being formed from the pluripotent stem cells in the bone marrow (Fig. 11-4). The red cell precursors move through a series of divisions, each producing a smaller cell as they continue to develop into mature red blood cells. Hemoglobin synthesis begins at the early erythroblast stage and continues until the cell becomes a mature erythrocyte. During its transformation from normoblast to reticulocyte, the red blood cell accumulates hemoglobin as the 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.[1] 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, and the reticulocyte count therefore 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, but is sensed by the kidneys, which produce and release a hormone called *erythropoietin* into the blood, and this hormone in turn stimulates erythropoiesis in the bone marrow. In the absence of erythropoietin, as in kidney failure, hypoxia has little or no effect on red blood cell production. Human erythropoietin can be produced by recombinant deoxyribonucleic acid (DNA) technology. It is used for the management of anemia in conditions such as chronic renal failure and chemotherapy-induced anemia in persons with cancer.

RED CELL DESTRUCTION

Mature red blood cells have a life span of approximately 4 months, or 120 days. Without DNA and ribonucleic acid (RNA), red blood cells cannot synthesize the proteins needed for cellular repair, growth, or renewal of enzymes. As the red blood cell ages, its metabolic activity decreases, its enzyme activity declines, and its nonreparable membrane becomes fragile and prone to rupture as it travels through narrow spaces in the circulation and small trabecular spaces in 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 accomplished by a group of large phagocytic cells found in the spleen, liver, bone marrow, and lymph nodes. During red blood cell destruction, amino acids from the globin chains and iron from the heme units are salvaged and reused, whereas the bulk of the heme unit is converted to bilirubin, the pigment of bile (Fig. 11-5). Bilirubin, which is insoluble in plasma, attaches to plasma proteins for transport to the liver, where it removed from the blood 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

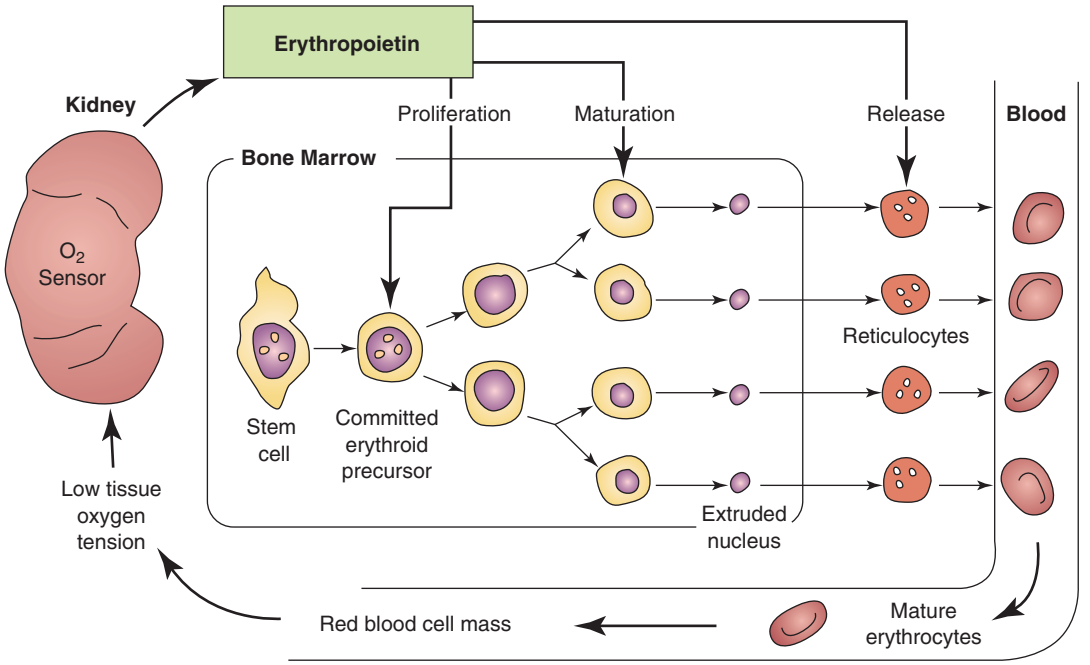

FIGURE 11-4 Red blood cell development. Committed bone marrow cells proliferate and differentiate through the erythroblast and normoblast stages to reticulocytes, which are released into the bloodstream and finally become erythrocytes.

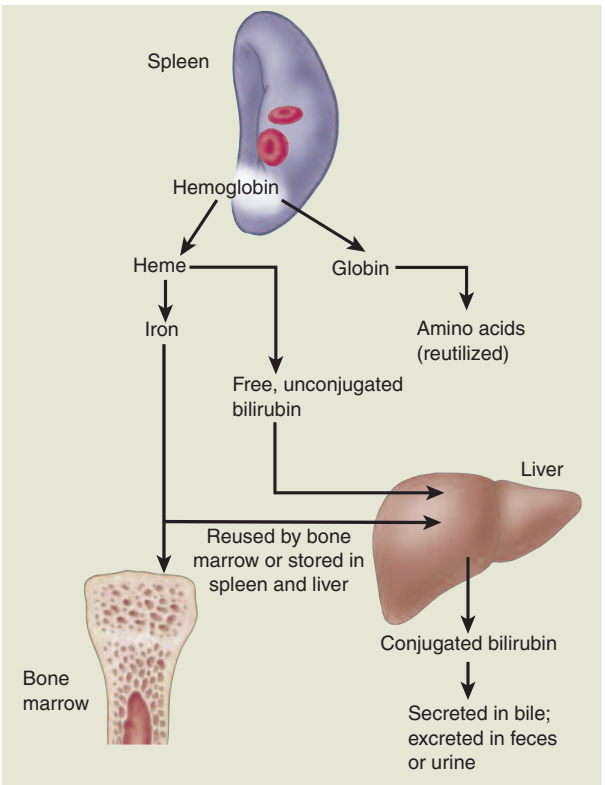

FIGURE 11-5 Destruction of red blood cells and fate of hemoglobin.

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 and other plasma proteins. 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

The red blood cell, which lacks mitochondria, relies on glucose and the glycolytic pathway for its metabolic needs (see Chapter 1). The enzyme-mediated anaerobic metabolism of glucose generates the adenosine triphosphate (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. A hereditary deficiency of glucose-6-phosphate dehydrogenase (G6PD; to be dis-

cussed) predisposes to oxidative denaturation of hemoglobin, with resultant red cell injury and lysis.

LABORATORY TESTS

Red blood cells can be studied by means of a sample of blood (Table 11-1). 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 mm^3 of blood. The *percentage of reticulocytes* (normally approximately 1%) provides an index of the rate of red cell production. The *hemoglobin* (grams per dL 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 percentage of red cell mass in 100 mL of blood (Fig. 11-6). 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, red blood cells with their hemoglobin provide the means for transporting oxygen from the lungs to the tissues. The biconcave shape of the red blood cell increases its surface area for diffusion, the thinness of the cell membrane allows oxygen to move readily to the interior of the cell, and the membrane structure of the red cell allows it to be deformed while moving through the smallest of capillaries. The hemoglobin molecule is composed of two pairs of α and β chains, each of which consists of a globin (protein) portion and heme unit, which surrounds an atom of iron that binds oxygen. 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 heme portion of the hemoglobin molecule is converted to bilirubin and its iron is salvaged and reused. 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.

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.

TABLE 11-1 Standard Laboratory Values for Red Blood Cells

Test	Normal Values	Significance
Red blood cell count (RBC)		
Men	4.2–5.4 × 10^6/μL	Number of red cells in the blood
Women	3.6–5.0 × 10^6/μL	
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

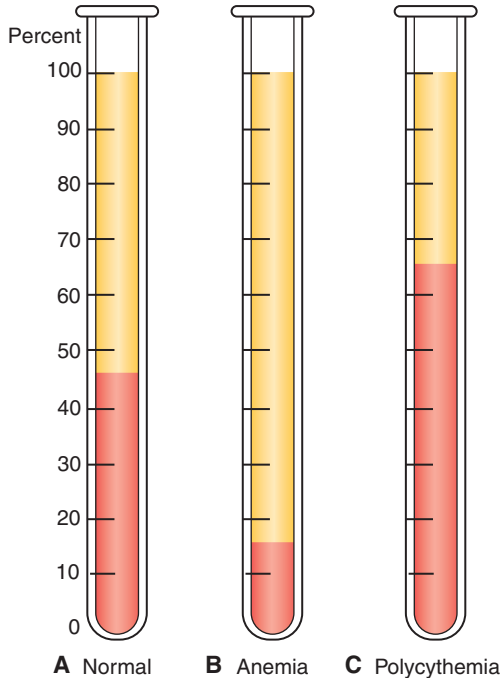

FIGURE 11-6 Hematocrit. The hematocrit measures the percentage of cells in 100 mL of blood: (**A**) normal, (**B**) decreased in anemia, and (**C**) increased in polycythemia.

KEY CONCEPTS

Anemia

- Anemia, which is a deficiency of red cells or hemoglobin, results from excessive loss (blood loss anemia), increased destruction (hemolytic anemia), or impaired production of red blood cells (iron-deficiency, megaloblastic, and aplastic anemias).
- Blood loss anemia is characterized by loss of iron-containing red blood cells from the body; hemolytic anemia involves destruction of red blood cells in the body with iron being retained in the body.
- Manifestations of anemia are caused by the decreased presence of hemoglobin in the blood (pallor), tissue hypoxia due to deficient oxygen transport (weakness and fatigue), and recruitment of compensatory mechanisms (tachycardia and palpitations) designed to increase oxygen delivery to the tissues.

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) those resulting from tissue hypoxia due to decreased oxygen delivery, (2) those due to compensatory mechanisms, and (3) the signs and symptoms associated with the pathologic process causing the anemia. The manifestations of anemia depend on its severity, the rapidity of its development, and the affected person's age and health status.[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 and faintness. 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 preexisting heart disease. Erythropoiesis is accelerated and may be recognized by diffuse bone pain and sternal tenderness. In addition to the common manifestations of anemia, hemolytic anemias are often accompanied by jaundice caused by increased blood levels of bilirubin. In aplastic anemia, petechiae and purpura (*i.e.*, red spots caused by small-vessel bleeding) are the result of reduced platelet function.

Laboratory tests are useful in determining the severity and cause of the anemia. The red cell count and hemoglobin levels provide information about the severity of the anemia, whereas red cell characteristics such as size (normocytic, microcytic, macrocytic), color (normochromic, hypochromic), and shape often provide information about the cause of anemia (Fig. 11-7).

BLOOD LOSS ANEMIA

The clinical and red cell manifestations associated with blood loss anemia depend on the rate of hemorrhage and whether the bleeding loss is internal or external. With rapid blood loss, circulatory shock and circulatory collapse may occur. With more slowly developing anemia, the amount of red cell mass lost may reach 50% without the occurrence of signs and symptoms.[1] The effects of acute blood loss are mainly due to loss of intravascular volume, which can lead to cardiovascular collapse and shock (see Chapter 19). A fall in the red blood cell count, hematocrit, and hemoglobin is caused by hemodilution resulting from movement of fluid into the vascular compartment. Initially, the red cells are normal in size and color (normocytic, normochromic). The hypoxia that results

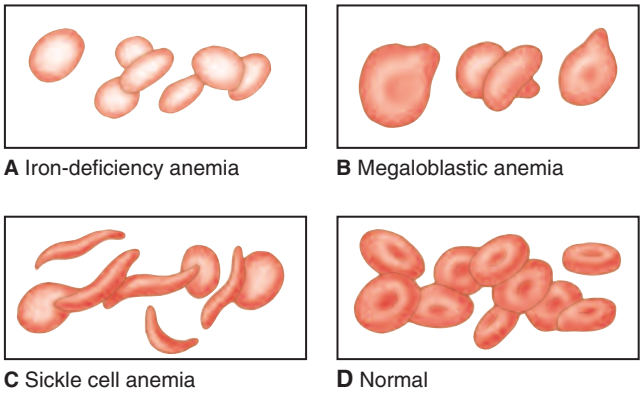

FIGURE 11-7 Red cell characteristics seen in different types of anemia: (**A**) microcytic and hypochromic red cells, characteristic of iron-deficiency anemia; (**B**) macrocytic and misshaped red blood cells, characteristic of megaloblastic anemia; (**C**) abnormally shaped red blood cells seen in sickle cell disease; and (**D**) normocytic and normochromic red blood cells, as a comparison.

from blood loss stimulates proliferation of committed erythroid stem cells in the bone marrow. It takes about 5 days for the progeny of stem cells to fully differentiate, an event that is marked by increased reticulocytes in the blood.[3] If the bleeding is controlled and sufficient iron stores are available, the red cell concentration returns to normal within 3 to 4 weeks. External bleeding leads to iron loss and possible iron deficiency, which can hamper restoration of red cell counts.

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 are commonly asymptomatic 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 ANEMIAS

Hemolytic anemia is characterized by the premature destruction of red cells, retention in the body of iron and other products of hemoglobin destruction, and an increase in erythropoiesis to compensate for the loss of 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.

As with physiologic destruction of senescent red cells, in the great majority of hemolytic anemias, the premature destruction of red cells occurs in the spleen (extravascular hemolysis). Much less commonly, red cell lysis occurs in the vascular compartment (intravascular hemolysis) and is related to acquired conditions such as mechanical injury, complement fixation, or exogenous toxic factors. Intravascular hemolysis is characterized by presence of hemoglobin in the blood (hemoglobinemia), hemoglobin in the urine (hemoglobinuria), the intracellular storage form of iron in the urine (hemosiderinuria), and jaundice. In extravascular hemolysis, premature destruction of red cells takes place in the thin-walled splenic sinusoids, a spongelike labyrinth of macrophages with long dendritic processes. It occurs whenever red cells are rendered "foreign" or become less deformable. Because extreme alterations in shape are required to navigate these sinusoids, cells with reduced deformability become sequestered and are phagocytosed by macrophages. With extravascular hemolysis, hemoglobinemia and hemoglobinuria are not observed, and the principal features are anemia and jaundice.

Hemolytic anemia can be further classified as to whether the underlying cause of the disorder is inherited or acquired. Inherited disorders include the inherited disorders of the red cell membrane, hemoglobinopathies (*e.g.*, sickle cell anemia and thalassemias), and inherited enzyme disorders. 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.

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 (*e.g.*, spectrin) that leads to the 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, jaundice, splenomegaly, 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

The hemoglobinopathies represent disorders of the hemoglobin molecule, most being caused by point mutations in a globin chain gene. The production of each type of globin chain is controlled by individual structural genes with five different gene loci. Mutations can occur anywhere in these five loci.

Sickle Cell Disease. Sickle cell disease is a chronic disorder resulting in anemia, and pain and organ failure due to vessel occlusion. Affected persons experience severe hemolytic anemia, chronic hyperbilirubinemia, and vaso-occlusive crises. Hemolysis produces an anemia with hematocrit values ranging from 18% to 30%.[4] The hyperbilirubinemia that results from the breakdown products

of hemoglobin often leads to jaundice and the production of pigment stones in the gallbladder.

Sickle cell disease is an inherited disease that is caused by the presence of an abnormal hemoglobin S (HbS), which upon deoxygenation transforms the erythrocyte into a sickle shape (see Fig. 11-7). HbS is transmitted by recessive inheritance and can manifest as sickle cell trait (*i.e.*, heterozygote with one HbS gene) or sickle cell disease (*i.e.*, homozygote with two HbS genes). Sickle cell disease affects approximately 50,000 (0.1% to 0.2%) African Americans, and about 10% of African Americans carry the trait.[4] In parts of Africa, where malaria is endemic, the gene frequency approaches 30%, attributed to the slight protective effect it confers against *Plasmodium falciparum* malaria.[5]

The abnormal structure in HbS 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 (Fig. 11-8). In the heterozygote, only approximately 40% of the hemoglobin is HbS, but in the homozygote, 80% to 95% of the hemoglobin is HbS. Variations in proportions exist, and the concentration of HbS correlates with the risk of sickling.[5] Under conditions of deoxygenation, HbS in the homozygote with sickle cell disease aggregates and polymerizes in the cytoplasm, creating a semisolid gel that changes the shape and deformability of the cell (see Fig. 11-7). The sickled cell may return to normal shape with oxygenation in the lungs. However, after repeated episodes of deoxygenation, the cells remain permanently sickled. The person with sickle cell trait who has less HbS has little tendency to sickle except during severe hypoxia and is virtually asymptomatic. Fetal hemoglobin (HbF), with its high affinity for oxygen, inhibits the polymerization of HbS; therefore, most infants with sickle cell disease do not begin to experience the effects of the sickling until sometime after 4 to 6 months of age, when the HbF has been replaced by HbS.

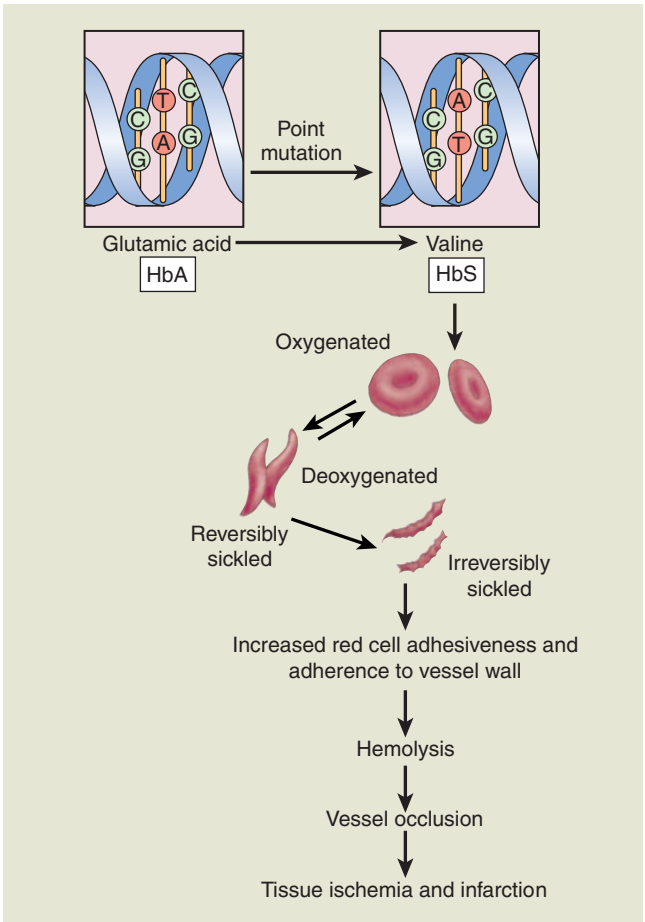

FIGURE 11-8 Mechanism of sickling and its consequences in sickle cell disease.

There are two major consequences of red blood cell sickling: hemolysis of the sickled cells and vessel occlusion (see Fig. 11-8). The increased rigidity of the sickled cells results in obstruction of the microcirculation and ischemic injury to many tissues. The inflexibility of the sickled cells also makes them more susceptible to destruction (hemolysis) during circulation through the spleen. The sickled cells also demonstrate membrane changes, leading to increased adhesiveness and adherence, producing further complications of capillary blood flow.[2]

Blood vessel occlusion causes most of the severe complications of sickle cell disease. An acute pain episode results from vessel occlusion and can occur suddenly in almost any part of the body.[6] Common sites obstructed by sickled cells include the abdomen, chest, bones, and joints. Many areas may be affected simultaneously. Infarctions caused by sluggish blood flow may 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 is the second leading cause of hospitalization in persons with sickle cell disease and is characterized by pulmonary infiltrates, shortness of breath, fever, chest pain, and cough.[6,7] The syndrome can cause chronic respiratory insufficiency and is a leading cause of death in sickle cell disease. Children may experience growth retardation and susceptibility to osteomyelitis. Painful bone crises may be caused by marrow infarcts of the bones of the hands and feet, resulting in swelling of those extremities. Twenty-five percent of persons with sickle cell disease have neurological complications related to vessel occlusion.[7] Stroke occurs in children 1 to 15 years of age and may recur in two thirds of those afflicted. Transient ischemic attack or cerebral hemorrhage may precede the stroke.

The spleen is especially susceptible to damage by HbS. 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.[8] 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 have not had time to create antibodies to these organisms and rely on the

spleen for their removal. In the absence of specific antibodies to the polysaccharide capsular antigens of these organisms, splenic activity is essential for removing these organisms when they enter the blood.

The factors associated with sickling and vessel occlusion include cold, stress, physical exertion, infection, and illnesses that cause hypoxia, dehydration, or acidosis. The rate of HbS polymerization is affected by the concentration of hemoglobin in the cell. Dehydration increases the hemoglobin concentration and contributes to the polymerization and resulting sickling. Acidosis reduces the affinity of hemoglobin for oxygen, resulting in more deoxygenated hemoglobin and increased sickling. Even such trivial incidents as reduced oxygen tension induced by sleep may contribute to the sickling process.

The signs and symptoms of sickle cell disease make their appearance during infancy. Neonatal diagnosis of sickle cell disease is made on the basis of clinical findings and hemoglobin solubility results, which are confirmed by hemoglobin electrophoresis. Prenatal diagnosis is done by the analysis of fetal DNA obtained by amniocentesis.[4]

In the United States, screening programs have been implemented to detect newborns with sickle cell disease and other hemoglobinopathies. Cord blood or heel stick samples are subjected to electrophoresis to separate the HbF from the small amounts of HbA and HbS. Other hemoglobins may be detected and quantified by further laboratory evaluation. Many states mandate neonatal screening of all newborns, regardless of ethnic origin. Ideally, the effective screening program also includes expert genetic counseling and education about pregnancy options.

There is no known cure for sickle cell anemia, so treatment to reduce symptoms includes pain control, hydration, and management of complications. The person is advised 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. 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.[9] Maintaining full immunization, including *H. influenzae* vaccine and hepatitis B vaccine, is recommended. The National Institutes of Health Committee on Management of Sickle Cell Disease also recommends administration of the 7-valent pneumococcal vaccine beginning at 2 to 6 months of age.[9] The 7-valent vaccine should be followed by immunization with the 23-valent pneumococcal vaccine at 24 months of age or later.

Hydroxyurea is a cytotoxic drug used to prevent complications of sickle cell disease. The drug allows synthesis of more HbF and less HbS, thereby decreasing sickling. Long-term effects on organ damage, growth and development, and risk of malignancies are unknown.[6] Bone marrow or stem cell transplantation has the potential for cure in symptomatic children but carries the risk of graft-versus-host disease.

Thalassemias. The thalassemias are a group of inherited disorders of hemoglobin synthesis due to absent or defective synthesis of the α or β chains of adult hemoglobin. 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 disease, the thalassemias occur with a high degree of frequency in certain populations. The β-thalassemias, sometimes called *Cooley anemia* or *Mediterranean anemia,* are most common in the Mediterranean 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 African Americans.

Two factors contribute to the anemia that occurs in thalassemia: (1) the direct effect of gene mutation on production of α or β chains of the hemoglobin molecule, and (2) the indirect effect resulting from the continued production of the unaffected chain. Defective production of α or β chains leads to deficient hemoglobin production and the development of a hypochromic microcytic anemia. Although there is impaired production of the affected chain, the unaffected type of chain continues to be synthesized and accumulates in the red cell, interfering with normal maturation, and generating oxygen free radicals that contribute to red cell hemolysis and anemia.

The β-*thalassemias* result from one of nearly 200 point mutations in the β-globin gene, causing a defect in β-chain synthesis.[10] In β-thalassemia, the excess α chains are denatured to form precipitates (*i.e.,* Heinz bodies) in the bone marrow red cell precursors. 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 destruction in the spleen. In addition to the anemia, persons with moderate to severe forms of the disease suffer from coagulation abnormalities. Thrombotic events (stroke and pulmonary embolism) appear to be related to altered platelet function, endothelial activation, and an imbalance of procoagulants and anticoagulants.[10]

The clinical manifestations of 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 anemia. Persons who are homozygous for the trait (thalassemia major) have severe, transfusion-dependent anemia that is evident at 6 to 9 months of age. If transfusion therapy is not started early in life, severe growth retardation occurs in children with the disorder. Increased hematopoiesis, in response to erythropoietin, causes bone marrow expansion, impairs bone growth, and causes bone abnormalities. Bone marrow expansion leads to thinning of the cortical bone, with new bone formation evident on the maxilla and frontal bones of the face (*i.e.,* chipmunk facies). The long bones, ribs, and vertebrae may become vulnerable to fracture. Splenomegaly and hepatomegaly result from increased red cell destruction. Iron overload is a major complication of β-thalassemia. Excess iron stores, which accumulate

from increased dietary absorption and repeated transfusions, are deposited in the myocardium, liver, and endocrine organs and induce organ damage. Cardiac and hepatic disease are common causes of death from iron overload. Disorders of the pituitary, thyroid, and adrenal glands and the pancreas result in significant morbidity.[11]

Frequent transfusions (every 3 to 4 weeks) prevent most of the complications, and iron chelation therapy can reduce the iron overload and extend life expectancy.[11] Bone marrow transplantation is a potential cure for some patients, particularly in younger persons with no complications of the disease or its treatment.[11] In the future, stem cell gene replacement may provide a cure for many with the disease.

The α-*thalassemias* are caused by a gene deletion that results in defective α-chain synthesis. Synthesis of the α-globin chains of hemoglobin is controlled by two pairs of genes; hence, α-thalassemia shows great variations in severity. Silent carriers who have a deletion of a single α-globin gene are asymptomatic, and those with deletion of two genes have mild hemolytic anemia. Deletion of three of the four α-chain genes lead to unstable aggregates of α chains called *hemoglobin H* (HbH). This disorder is the most important clinical form and is common in Asians. 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 chronic moderate hemolytic anemia and may require transfusions during febrile illnesses or with certain medications.[11] The most severe form of α-thalassemia occurs in infants in whom all four α-globin genes are deleted. Such a defect results in a hemoglobin molecule (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. This disorder usually results in death in utero or shortly after birth.[10]

Inherited Enzyme Defects

The most common inherited enzyme defect that results in hemolytic anemia is a deficiency of G6PD. The gene that determines this enzyme is located on the X chromosome, and the defect is expressed only in males and homozygous females. There are more than 350 genetic variants of this disorder found in all populations. The African variant has been found in 10% of African Americans.[2] The disorder makes red cells more vulnerable to oxidants and causes direct oxidation of hemoglobin to methemoglobin and the denaturing of the hemoglobin molecule to form Heinz bodies, which are precipitated in the red blood cell. Hemolysis usually occurs as the damaged red blood cells move through the narrow vessels of the spleen, causing hemoglobinemia, hemoglobinuria, and jaundice. The hemolysis is short-lived, occurring 2 to 3 days after the trigger event. In persons of African descent, 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, nitrofurantoin, aspirin, phenacetin, some chemotherapeutic agents, and other drugs cause hemolysis. Free radicals generated by phagocytes during infections also are possible triggers. A more severe deficiency of G6PD is found in people of Mediterranean descent (*e.g.,* Sardinians, Sephardic Jews, Arabs). In some of these persons, chronic hemolysis occurs in the absence of exposure to oxidants. The disorder can be diagnosed through the use of a G6PD assay or screening test.

Acquired Hemolytic Anemias

Several acquired factors exogenous to the red blood cell produce 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. Obstructions 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 or destroy the red cell membrane. Antibodies may be produced by a person in response to drugs and disease (autoantibodies) or may come from an exogenous source (alloantibodies), such as those that 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) and sometimes IgA types, which are maximally active at 37°C, and cold-reacting antibodies of the IgM type, which are optimally active at or near 4°C.[2]

The warm-reacting antibodies react with antigens on the red cell membrane, causing destructive changes that lead to spherocytosis, with subsequent phagocytic destruction in the spleen or liver. They lack specificity for the ABO antigens but may react with the Rh antigens. The reactions are typically of rapid onset that may be life threatening in severity. Patients complain of fatigue and may present with angina or heart failure. On physical examination, jaundice and splenomegaly are usually present. There are varied causes. In approximately half the cases, the cause is idiopathic or unknown, and the other half are related to cancers of the lymphoproliferative system (*e.g.,* chronic lymphocytic leukemia, lymphoma), collagen diseases (*e.g.,* systemic lupus erythematosus), viral infections, and inflammatory disorders (*e.g.,* ulcerative colitis).[2] The antihypertensive drug α-methyldopa and the antiarrhythmic drug quinidine account for a small number of cases.[2] The drug-induced hemolysis is commonly benign.

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 tempera-

ture may fall below 30°C. Vascular obstruction by red cells results in pallor, cyanosis of the body parts exposed to cold temperatures, and Raynaud phenomenon (see Chapter 17). Hemolytic anemia caused by cold-reacting antibodies develops in only a few persons and is rarely severe.

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. The direct antiglobulin test detects the antibody on red blood cells and is positive in cases of autoimmune hemolytic anemia, erythroblastosis fetalis (*i.e.*, Rh disease of the newborn), transfusion reactions, and drug-induced hemolysis. The indirect antiglobulin test detects antibody in the serum, and the result is positive for specific antibodies. It is used for antibody detection and cross-matching before transfusion.

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 demand. 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 toddlers, adolescents, and women of childbearing age.

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.[12] 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. In the postnatal period, lactation requires approximately 1 mg of iron daily.[12]

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.[13]

Iron-deficiency anemia is characterized by low hemoglobin and hematocrit levels, 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 (see Fig. 11-7). 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 impaired oxygen transport and lack of hemoglobin. Depending on the severity of the anemia, fatigability, palpitations, dyspnea, angina, and tachycardia may occur. Epithelial atrophy is common and results in waxy pallor, brittle hair and nails, smooth tongue, sores in the corners of the mouth, and sometimes in 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. Iron deficiency in children may also result in neurologic manifestations such as developmental delay, stroke, and cranial nerve palsies.[14]

Prevention of iron deficiency is a primary concern in infants and children. Iron supplementation is recommended at 4 to 6 months of age in breast-fed infants, and use of iron-fortified formulas (rather than cow's milk) and cereals is recommended for infants younger than 1 year of age.[15] In the second year, a diet rich in iron-containing foods and use of iron-fortified vitamins will help prevent iron deficiency. 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 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 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 produce some 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. 11-9). The vitamin B_{12}–intrinsic factor complex travels to the ileum, where membrane receptors allow the binding of the complex to the epithelial cells. Vitamin B_{12} is then separated from intrinsic factor and transported across the membrane into the circulation. There it is bound to its carrier protein, transcobalamin II, which transports vitamin B_{12} to its storage and tissue sites. Any defects in this pathway may cause a vitamin B_{12} deficiency. An important cause of vitamin B_{12} deficiency is pernicious anemia, resulting from a hereditary atrophic gastritis. As discussed in Chapter 28, 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, inflammation or neoplasms in the terminal ileum, and malabsorption syndromes in which vitamin B_{12} and other B-vitamin compounds are poorly absorbed.

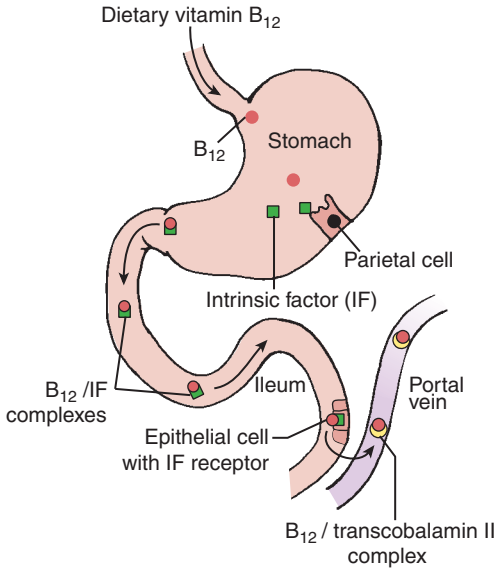

FIGURE 11-9 Schematic illustration of vitamin B_{12} absorption.

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 RNA production of hemoglobin and structural protein (see Fig. 11-7). The cells have immature nuclei and show evidence of cellular destruction. 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.

Vitamin B_{12} deficiency is diagnosed 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, has been commonly used in the past to document decreased absorption of vitamin B_{12}. Currently, the diagnosis of pernicious anemia is usually made by the detection of parietal cell and intrinsic factor antibodies.[16] Lifelong treatment consisting of intramuscular injections of vitamin B_{12} reverses the anemia and improves the neurologic changes.

Folic Acid–Deficiency Anemia. Folic acid (folate) is also required for DNA synthesis and red cell maturation, and its deficiency produces the same type of megaloblastic 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. Much of the vitamin, however, 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. Total body stores of folic acid amount to 2000 to 5000 micrograms (μg), and 50 μg is required in the daily diet.[3] A dietary deficiency may result in anemia in a few months. Malabsorption of folic acid may be due to syndromes such as sprue or other intestinal disorders. 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. In neoplastic disease, tumor cells compete for folate, and deficiency is common. 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.[17] The U.S. Public Health Service recommends

that all women of childbearing age should take 400 μg of folic acid daily. It is estimated that 50% of neural tube defects could thus be prevented.[18] To ensure adequate folate consumption, the U.S. Food and Drug Administration mandated the addition of folate to cereal grain products effective January 1, 1998.

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.

The causes of aplastic anemia include 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, which causes anemia, thrombocytopenia, and neutropenia. 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 a drug is initiated. Such reactions often are severe and sometimes irreversible and fatal. Aplastic anemia can also 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*.

For young and severely affected individuals, the treatment of aplastic anemia can include the use of stem cell replacement by bone marrow or peripheral blood transplantation. Histocompatible donors supply the stem cells to replace the patient's destroyed marrow cells. Graft-versus-host disease, rejection, and infections are major risks of the procedure, yet 70% or more survive.[19] 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 up to 50% of patients.[19] 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 tuberculosis, AIDS, osteomyelitis, rheumatoid arthritis, systemic lupus erythematosus, and Hodgkin disease. It is thought that the short life span, deficient red cell production in response to erythropoietin, 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. The lymphocytes release cytokines (*e.g.*, interleukin-1 and interferon) that suppress the erythropoietin response, inhibit erythroid precursors, and reduce iron transport.[20] The moderate to severe anemia is similar to iron-deficiency anemia with microcytic, hypochromic red cells. The anemia may be reversed when the underlying disease is treated, or with erythropoietin therapy.[20]

Chronic renal failure almost always results in a normocytic, normochromic anemia, primarily because of a deficiency of erythropoietin. Unidentified uremic toxins and retained nitrogen also interfere with the actions of erythropoietin, and red cell production and survival. Hemolysis and blood loss associated with hemodialysis and bleeding tendencies also contribute to the anemia of renal failure. In persons whose hematocrits are 30% to 35%, recombinant erythropoietin injected several times a week eliminates the need for transfusions.[20] Oral iron is sometimes required for a good response.

In summary, anemia is a condition of an abnormally low number of circulating red blood cells or low hemoglobin level, or both. It is not a disease, but manifestation of a disease process or alteration in body function. Anemia can result from excessive blood loss, red cell destruction due to 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 deficiencies 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 are those associated with impaired oxygen transport; alterations in red blood cell number, hemoglobin content, and cell structure; and the signs and symptoms of the underlying process causing the anemia.

Polycythemia

Polycythemia is an abnormally high total red blood cell mass with a hematocrit greater than 50%. It is categorized as relative or absolute. 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.

Absolute polycythemia is a rise in hematocrit due to an increase in total red cell mass and is classified as primary or secondary. 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. Viscosity rises exponentially with the hematocrit and interferes with cardiac output and blood flow. Hypertension is common and there may be complaints of headache, inability to concentrate, and some difficulty with hearing and vision because of decreased cerebral blood flow. 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. Thromboembolism occurs in 15% to 60% of persons with polycythemia vera and contributes to death in 10% to 40% of the cases.[21] Hemorrhage, due to platelet abnormalities, occurs in 15% to 35% of cases and is also an important cause of death. 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.

Secondary polycythemia results from a physiologic increase in the level of erythropoietin, commonly as a compensatory response to hypoxia. Conditions causing hypoxia include living at high altitudes, chronic heart and lung disease, and smoking. The resultant release of erythropoietin by the kidney causes the increased formation of red blood cells in the bone marrow. Neoplasms that secrete erythropoietin may also cause a secondary polycythemia. 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 11-2). Hemoglobin concentrations at birth are high, reflecting the high synthetic activity in utero to provide adequate oxygen delivery. Toward the end of the first postnatal week, hemoglobin concentration begins to decline, gradually falling to a minimum value at approximately 2 months of age.[22] 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 averages about 70% of the total hemoglobin and declines to trace amounts by 6 to 12 months of age.[22] The switch to HbA provides greater unloading of oxygen to the tissues because HbA has a lower affinity for oxygen compared with HbF. Infants who are small for gestational age, born to diabetic or smoking mothers, or who experienced hypoxia in utero

TABLE 11-2 Red Cell Values for Term Infants

Age	RBC × 10^6/μL 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.)

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. A contributing factor is the frequent blood sampling that is often necessary to stabilize these infants.[22] 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 below 33%, the clinical features are more evident.

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 are jaundiced.[23] This physiologic jaundice appears in term infants on the second or third day of life. Ordinarily, the indirect bilirubin in umbilical cord blood is 1 to 3 mg/dL and rises at a rate of less than 5 mg/dL in 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.[23] 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 slower rise and longer duration in serum bilirubin levels, perhaps because of poor hepatic uptake and reduced albumin binding of bilirubin. Most neonatal jaundice resolves within 1 week and is untreated.

Many factors can contribute to elevated bilirubin levels in the neonate, including 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.[23] These neonates accumulate significant levels of unconjugated bilirubin 7 days after birth and reach maximum levels of 10 to 30 mg/dL in 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. Nursing 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. Asphyxia and hyperosmolality may also contribute by damaging the blood-brain barrier and allowing bilirubin to cross and enter the cells. The level of unconjugated bilirubin and the duration of exposure that will be toxic to the infant are unknown. The less mature infant, however, is at greater risk for kernicterus.[23] The manifestations of kernicterus may appear 2 to 5 days after birth in term infants or by day 7 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 are seriously damaged and by

3 years of age exhibit involuntary muscle spasm, seizures, mental retardation, and deafness.

The diagnosis of neonatal jaundice is made on the basis of history and clinical and laboratory findings. Treatment usually consists of phototherapy. Exposure to fluorescent light in the blue range of the visible spectrum (420- to 470-nm wavelength) reduces bilirubin levels.[23] 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. Effective treatment depends on the area of skin exposed and the infant's ability to metabolize and excrete bilirubin. Frequent monitoring of bilirubin levels, body temperature, and hydration is critical to the infant's care. 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 a danger of kernicterus developing in the infant, resulting in severe brain damage or death.

Several advances have served significantly to 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 in the first trimester using fetal blood or amniotic cells.[24] 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

Anemia is an increasingly common health problem in the elderly, affecting approximately 12% of persons aged 60 years and older.[25] Its prevalence is known to increase with age, the highest prevalence occurring in men aged 85 years and older. Undiagnosed and untreated anemia can have severe consequences and is associated with increased risk of mortality, lower functional ability, self-care deficits, and depression. It can also cause neurologic and cognitive disorders and cardiovascular complications.

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 g/dL.[26] In most asymptomatic elderly persons, lower hemoglobin levels result from iron deficiency and anemia of chronic disease. Anemia of chronic disease is associated with a number of conditions such as acute infections, chronic infections (tuberculosis), chronic inflammatory disorders (rheumatoid arthritis), malignancy, and protein-calorie malnutrition.[25]

As with other body systems, the capacity for red cell production changes with aging. The location of bone cells involved in red cell production shifts toward the axial skeleton and the number of progenitor cells declines from approximately 50% at age 65 to approximately 30% at age 75 years.[26] Despite these changes, the elderly are able to maintain hemoglobin and hematocrit levels within a range that is similar to that in younger adults.[27] However, during a stress situation such as bleeding, the red blood cells of the elderly are not replaced as promptly as those of their younger counterparts. This inability to replace red blood cells closely correlates with the increased prevalence of anemia in the elderly.

Although the age-associated decline in the hematopoietic reserve in the elderly is not completely understood, several factors seem to play a role, including a reduction in hematopoietic progenitors, reduced production of hematopoietic growth factors, and reduced sensitivity of hematopoietic progenitors (*e.g.,* erythropoietin).[25,28] Inflammatory cytokines, which have been found to increase with age, may mediate this reduced sensitivity to erythropoietin.

The diagnosis of anemia in the elderly requires a complete physical examination, a complete blood count, and studies to rule out comorbid conditions such as malignancy, gastrointestinal conditions that cause bleeding, and pernicious anemia. The complete blood count should include a peripheral blood smear and a reticulocyte count and index. If the reticulocyte index is appropriately increased for the level of anemia, then blood loss or red cell destruction should be suspected. If the reticulocyte index is inappropriately low, then decreased red cell production is indicated.[28]

The treatment of anemia in the elderly should focus on the underlying cause and correction of the red cell deficit. An important aspect of anemia of chronic disease is the inability to use and mobilize iron effectively.[25] Orally administered iron is poorly used in older adults, despite normal iron absorption.[26] Although erythropoietin remains the treatment of choice for anemias associated with cancer and renal disease, its potential use in treating anemias associated with aging remains to be established.

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, it 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.

Anemia is an increasingly common health problem in the elderly, affecting approximately 12% of persons aged 60 years and older. As with cells in other tissues, the capacity for red cell replacement decreases with aging. Although most elderly persons are able to maintain their hemoglobin and hematocrit levels within a normal range, they are unable to replace their red cells as promptly as their younger counterparts during a stress situation such as bleeding. This inability to replace red blood cells closely correlates with the increased prevalence of anemia in the elderly, which is usually the result of bleeding, infection, malignancy, or chronic disease.

Review Exercises

A 29-year-old woman complains of generalized fatigue. Her physical examination reveals a heart rate of 115 beats/minute, BP 115/75, and respiratory rate of 28 breaths/minute. Her skin and nail beds are pale. Her laboratory results include RBC 3.0×10^6/μL, hematocrit 30%, hemoglobin 9 g/dL, and decreased serum ferritin levels.

A. What disorder do you suspect this woman has?
B. What additional data would be helpful in determining the etiology of her condition?
C. Which of her signs reflect the body's attempt to compensate for the disorder?
D. What is the significance of the low ferritin level, and how could it be used to make decisions related to her treatment?

A 65-year-old woman is being seen in the clinic because of numbness in her lower legs and feet and difficulty in walking. She has no other complaints. She takes a blood pressure pill, two calcium pills, and a multivitamin pill daily. Her laboratory results include RBC 3.0×10^6/μL, hematocrit 20%, hemoglobin 9 g/dL, and a markedly elevated MVC.

A. What type of anemia does she have?
B. What is the reason for her neurologic symptoms?
C. What type of treatment would be appropriate?

A 12-year-old boy with sickle cell disease presents in the emergency department with severe chest pain. His mother reports that he was doing well until he came down with a respiratory tract infection. She also says he insisted on playing basketball with the other boys in the neighborhood even though he wasn't feeling well.

A. What is the most likely cause of pain in this boy?
B. Infections and aerobic-type exercise that increase the levels of deoxygenated hemoglobin produce sickling in persons who are homozygous for the sickle cell gene and have sickle cell disease, but not in persons who are heterozygous and have sickle cell trait. Explain.
C. People with sickle cell disease experience anemia but not iron deficiency. Explain.

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