

lack A and B antigens and therefore are considered *universal donors*. Persons with type AB blood are universal recipients. Signs of a transfusion reaction include a feeling of warmth in the involved vein, flushed face, headache, fever and chills, pain in the chest and abdomen, decreased blood pressure, and rapid pulse.

Another inherited factor in blood is the Rh factor, which may cause blood incompatibility if the mother is Rh-negative and the fetus is Rh positive (see Fig. 22-2). Rh blood incompatibility between maternal and fetal blood is reviewed in Chapter 22.

Plasma or colloidal volume-expanding solutions can be administered without risk of a reaction because they are free of antigens and antibodies.

### Diagnostic Tests

The basic diagnostic test for blood is the complete blood count (CBC), which includes total RBCs, WBCs, platelet counts, and **morphology** (size and shape), a differential count for WBCs, hemoglobin, and hematocrit values (see normal values inside the front cover of this book). These tests are useful screening tools. For example, **leukocytosis**, an increase in WBCs in the circulation, is often associated with inflammation or infection. **Leukopenia**, a decrease in leukocytes, occurs with some viral infections as well as with radiation and chemotherapy. An increase in eosinophils is common with allergic responses. The characteristics of the individual cells observed in a blood smear, including size and shape, uniformity, maturity, and amount of hemoglobin, are very important. Different types of anemia are distinguished by the characteristic size and shape of the cell, and presence of a nucleus in the RBC. More specialized tests are available. A summary of the most common diagnostic tests is provided in Ready Reference 5.

The hematocrit shows the percentage of blood volume composed of RBCs and indicates fluid and cell content. It may be an indicator of anemia, a low RBC count. Hemoglobin is measured, and the amount of hemoglobin per cell is shown by the mean corpuscular volume (MCV). MCV indicates the oxygen-carrying capacity of the blood.

Bone marrow function can be assessed by the **reticulocyte** (immature non-nucleated RBC) count, plus a bone marrow aspiration and biopsy.

Chemical analysis of the blood can determine the serum levels of such components as iron, vitamin B<sub>12</sub> and folic acid, cholesterol, urea, glucose, and bilirubin. The results can indicate metabolic disorders and disorders within various other body systems.

Blood-clotting disorders can be differentiated by tests such as bleeding time (measures platelet function—the time to plug a small puncture wound); prothrombin time or INR International Normalized Ratio (measures the extrinsic pathway); and partial thromboplastin time (PTT—intrinsic pathway), which measure the function of various factors in the coagulation process. They are

also used to monitor anticoagulant therapy. The reference values for these tests are best established for individual patients based on their health history.

### Blood Therapies

- Whole blood, packed red blood cells, or packed platelets may be administered when severe anemia or thrombocytopenia develops.
- Plasma or colloidal volume-expanding solutions can be administered without risk of a reaction because they are free of antigens and antibodies.
- Artificial blood products are available, but none can perform all the complex functions of normal whole blood. They are compatible with all blood types. Hemolink is made from human hemoglobin, whereas Hemopure is made from cow hemoglobin. Oxygent is a synthetic, genetically engineered blood substitute. Other agents, such as MP4, which is undergoing clinical trials, is combined with blood to improve the oxygen transfer from RBCs to tissues. Polyethylene glycol (PEG) is also being tested by various companies to bind and stabilize hemoglobin molecules, thus decreasing the problem of the disassociation of hemoglobin that occurs in storage. Although promising, none of these artificial blood products have yet received approval from the United States Food and Drug Administration (USFDA).
- Epoetin alfa (Procrit, Eprex) is a form of erythropoietin produced through the use of recombinant DNA technology. It may be administered by injection to stimulate production of red blood cells before certain surgical procedures (e.g., hip replacement) and for patients with anemia related to cancer or chronic renal failure. This reduces the risks of infection or immune reaction associated with multiple blood transfusions.
- Bone marrow or stem cell transplants are used to treat some cancers, severe immune deficiency, or severe blood cell diseases. For success, a close match in tissue or human leukocyte antigen (HLA) type is required. The marrow stem cells are extracted from the donor's pelvic bone, filtered, and infused into the recipient's vein. Normal cells should appear in several weeks. In cases of malignant disease, pretreatment with chemotherapy or radiation is required to destroy tumor cells before the transplant.
- For patients suffering from a lack of blood clotting capability, there are drugs available to aid in the clotting process. Nplate is a drug that has been recently approved by the FDA that directly stimulates platelet production by the bone marrow. NovoSeven is a drug developed primarily to treat hemophiliacs, but it has been adapted for use in treating combat trauma. Although these drugs are in use today, problems with unintentional clots that may form during their use continues to be a dangerous problem that must be considered.

### THINK ABOUT 10-2

- State the function of each type of cell in the blood.
- State three major functions of plasma proteins and list the component responsible for each.
- What is the normal pH range of blood? Why is it important to maintain this pH?
- Describe the three stages of hemostasis.

## Blood Dyscrasias

### The Anemias

Anemias cause a reduction in oxygen transport in the blood due to a decrease in hemoglobin content. The low hemoglobin level may result from declining production of the protein, a decrease in the number of erythrocytes, or a combination of these factors. Anemias may be classified by typical cell characteristics such as size and shape (morphology) or by etiology, for example, the hemolytic anemias.

The oxygen deficit leads to a sequence of events:

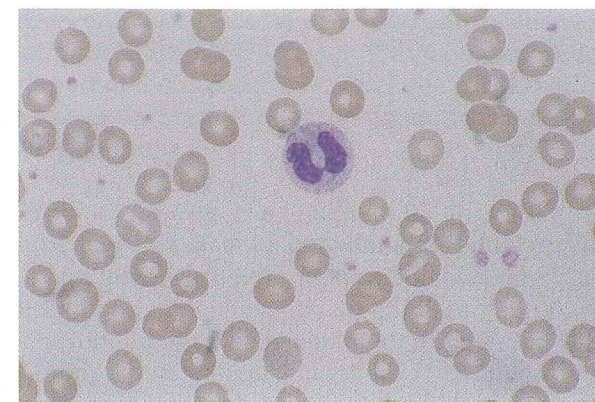
- Less energy is produced in all cells; cell metabolism and reproduction are diminished.
- Compensation mechanisms to improve the oxygen supply include tachycardia and peripheral vasoconstriction.
- These changes lead to the general signs of anemia, which include fatigue (excessive tiredness), **pallor** (pale face), **dyspnea** (increased effort to breathe), and **tachycardia** (rapid heart rate).
- Decreased regeneration of epithelial cells causes the digestive tract to become inflamed and ulcerated, leading to **stomatitis** (ulcers in the oral mucosa), inflamed and cracked lips, and dysphagia (difficulty swallowing); the hair and skin may show degenerative changes.
- Severe anemia may lead to angina (chest pain) during stressful situations if the oxygen supply to the heart is sufficiently reduced. Chronic severe anemia may cause congestive heart failure.

Anemias may occur when there is a deficiency of a required nutrient, bone marrow function is impaired, or blood loss or excessive destruction of erythrocytes occurs. This section of the chapter covers a few examples of different types of anemias.

### Iron Deficiency Anemia

#### ■ Pathophysiology

Insufficient iron impedes the synthesis of hemoglobin, thereby reducing the amount of oxygen transported in the blood (see Fig. 10-16A for a diagram showing four heme groups). This results in **microcytic** (small cell), **hypochromic** (less color) erythrocytes owing to a low concentration of hemoglobin in each cell (see Fig. 10-12). Iron deficiency anemia is very common; it ranges from mild to severe and occurs in all age groups. An



**FIGURE 10-12** Iron deficiency anemia shown in a blood smear. (From Stevens ML: Fundamentals of Clinical Hematology, Philadelphia, 1997, Saunders.)

estimated one in five women is affected, and the proportion increases for pregnant women. Because iron deficiency anemia is frequently a sign of an underlying problem, it is important to determine the specific cause of the deficit. There is also a reduction in stored iron, as indicated by decreased serum ferritin, decreased hemosiderin, and decreased iron-containing histiocytes in the bone marrow.

#### ■ Etiology

An iron deficit can occur for many reasons:

- Dietary intake of iron-containing vegetables or meat may be below the minimum requirement, particularly during the adolescent growth spurt or during pregnancy and breastfeeding, when needs increase. Normally, only 5% to 10% of ingested iron is absorbed, but this can increase to 20% when there is a deficit.
- Chronic blood loss from a bleeding ulcer, hemorrhoids, cancer, or excessive menstrual flow is a common cause of iron deficiency. Continuous blood loss, even small amounts of blood, means that less iron is recycled to maintain an adequate production of hemoglobin (Fig. 10-13).
- Duodenal absorption of iron may be impaired by many disorders, including **malabsorption** syndromes such as regional ileitis and **achlorhydria** (lack of hydrochloric acid in the stomach).
- Severe liver disease may affect both iron absorption and iron storage. An associated protein deficit would further impede hemoglobin synthesis.
- In the form of iron deficiency anemia associated with some infections and cancers, iron is present but is not well used, leading to low hemoglobin levels but high iron storage levels.

#### ■ Signs and Symptoms

Mild anemias are frequently asymptomatic. As the hemoglobin value drops, the general signs of anemia become apparent:



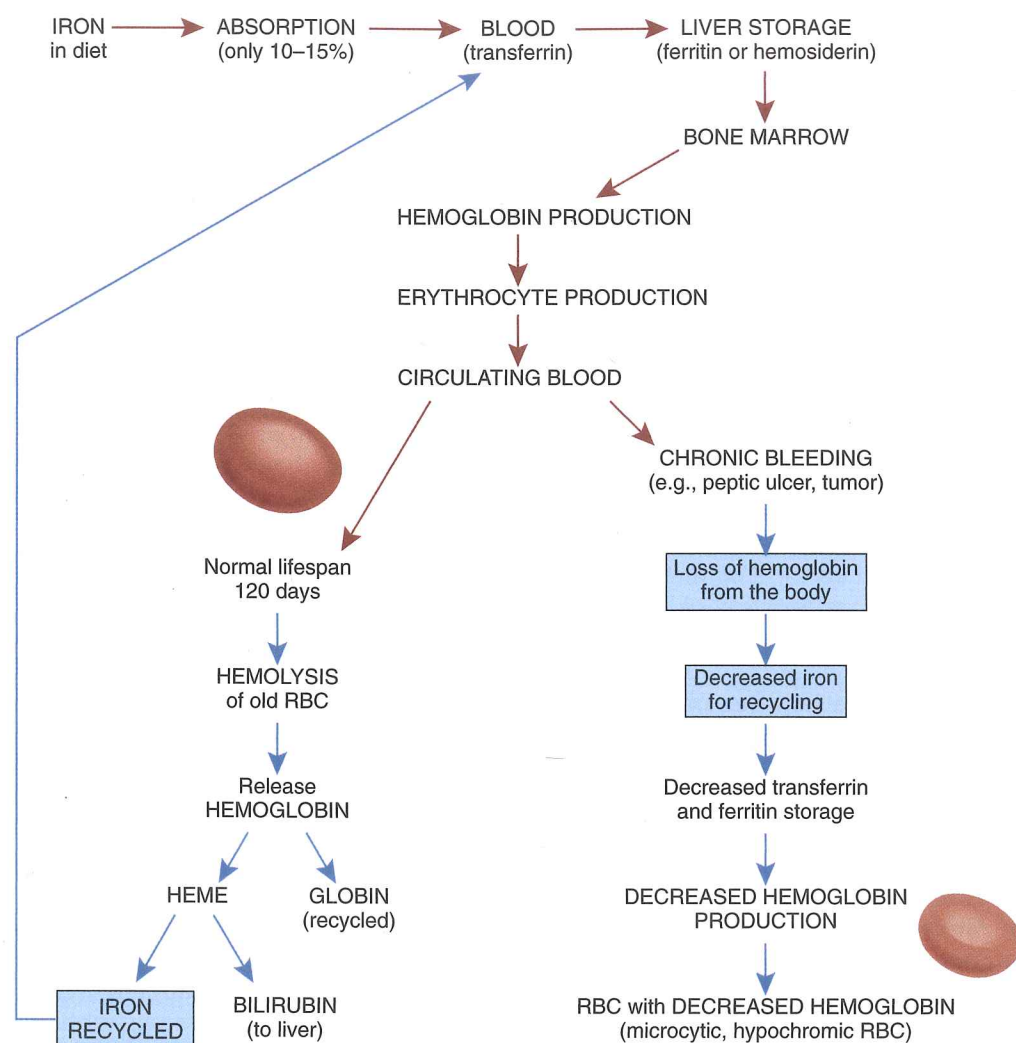


FIGURE 10-13 Iron deficiency anemia related to blood loss.

- Pallor of the skin and mucous membranes related to cutaneous vasoconstriction
- Fatigue, lethargy, and cold intolerance as cell metabolism decreases
- Irritability, a central nervous system response to hypoxia
- Degenerative changes, such as brittle hair, spoon-shaped (concave) and ridged nails
- Stomatitis and **glossitis**, inflammation in the oral mucosa and tongue, respectively
- Menstrual irregularities
- Delayed healing
- Tachycardia, heart palpitations, dyspnea, and perhaps **syncope** (fainting) as the anemia becomes more severe

#### ■ Diagnostic Tests

Laboratory tests demonstrate low values for hemoglobin, hematocrit, mean corpuscular volume and mean corpuscular hemoglobin, serum ferritin and serum iron, and transferrin saturation. On microscopic examination the erythrocytes appear hypochromic and microcytic.

#### ■ Treatment

The underlying cause must be identified and resolved if possible. The treatment and prognosis depend on the cause. Iron-rich foods or iron supplements in the least irritating and most easily absorbable forms for the individual may be given. It is advisable to take iron with food to reduce gastric irritation and nausea. Iron supplements usually lead to constipation. Liquid iron mixtures stain teeth and dentures, and therefore a straw should be used for drinking the medication.

#### THINK ABOUT 10-3

- Explain how chronic bleeding leads to iron deficiency anemia.
- Explain the signs of anemia that indicate compensation for hypoxia is occurring.
- Explain how the destruction of acid-producing cells in the stomach can lead to iron deficiency anemia.

### Pernicious Anemia-Vitamin B<sub>12</sub> Deficiency (Megaloblastic Anemia)

Megaloblastic anemias, as the name implies, are characterized by very large, immature, nucleated erythrocytes. This type of anemia usually results from a deficit of folic acid (vitamin B<sub>9</sub>) or vitamin B<sub>12</sub> (cyanocobalamin). Vitamin deficiencies usually develop gradually. There is now an increased interest in the folic acid deficiency that may occur during the first 2 months of pregnancy, resulting in an increased risk of spina bifida and other spinal abnormalities in the child. It is recommended that women in the childbearing years take folic acid supplements. Folic acid deficits are usually diet related.

The prototype of megaloblastic anemia in this chapter is pernicious anemia, a vitamin B<sub>12</sub> deficiency.

#### ■ Pathophysiology

Pernicious anemia is the common form of megaloblastic anemia that is caused by the malabsorption of vitamin B<sub>12</sub> owing to a lack of intrinsic factor (IF) produced in the glands of the gastric mucosa (Fig. 10-14). Intrinsic factor must bind with vitamin B<sub>12</sub> to enable absorption of the vitamin in the lower ileum. An additional problem occurs with the atrophy of the mucosa because the parietal cells can no longer produce hydrochloric acid. Achlorhydria interferes with the early digestion of protein in the stomach and with the absorption of iron; thus, an iron deficiency anemia may be present as well.

A deficit of vitamin B<sub>12</sub> leads to impaired maturation of erythrocytes owing to interference with DNA synthesis. The RBCs are very large (**megaloblasts** or **macrocytes**) and contain nuclei (Fig. 10-15). These large erythrocytes are destroyed prematurely, resulting in a low erythrocyte count, or anemia. The hemoglobin in the RBCs is normal and is capable of transporting oxygen. Often the maturation of granulocytes is also affected, resulting in development of abnormally large hypersegmented neutrophils. Thrombocyte levels may be low. In addition, lack of vitamin B<sub>12</sub> is a direct cause of **demyelination** of the peripheral nerves and eventually of the spinal cord. Loss of myelin interferes with conduction of nerve impulses and may be irreversible. Sensory fibers are affected first, followed by motor fibers.

#### ■ Etiology

- Dietary insufficiency is rarely a cause of this anemia because very small amounts of vitamin B<sub>12</sub> are required. Because the source of the vitamin is animal foods, vegetarians and vegans must ensure they include a source in their daily intake.
- The most common cause of vitamin B<sub>12</sub> deficiency is malabsorption, which may result from an autoimmune reaction, particularly in older individuals; from chronic gastritis, which is common in alcoholics and causes atrophy of the gastric mucosa; or from inflammatory conditions such as regional ileitis.

- The condition may also be an outcome of such surgical procedures as **gastrectomy** (removal or resection of part of the stomach), in which the parietal cells are removed, or resection of the ileum, which is the site of absorption.

#### ■ Signs and Symptoms

The basic manifestations of anemia are listed earlier. In addition, pernicious anemia has the following distinctive signs:

1. The tongue is typically enlarged, red, sore, and shiny.
2. The decrease in gastric acid leads to digestive discomfort, often with nausea and diarrhea.
3. The neurologic effects include tingling or burning sensations (paresthesia) in the extremities or loss of coordination and ataxia.

#### ■ Diagnostic Tests

- The erythrocytes appear macrocytic or megaloblastic and nucleated on microscopic examination and are reduced in number in the peripheral blood.
- The bone marrow is hyperactive, with increased numbers of megaloblasts. Granulocytes are hypersegmented and are decreased in number.
- The vitamin B<sub>12</sub> level in the serum is below normal. In Schilling's test, an oral dose of radioactive vitamin B<sub>12</sub> is used to measure absorption.
- The presence of hypochlorhydria or achlorhydria confirms the presence of gastric atrophy.

#### ■ Treatment

Oral supplements are recommended as prophylaxis for pregnant women and vegetarians. Vitamin B<sub>12</sub> is administered by injection as replacement therapy for people with pernicious anemia. Prompt diagnosis and treatment of pernicious anemia prevents cardiac stress and neurologic damage.

#### THINK ABOUT 10-4

- Explain why individuals with pernicious anemia have a low hemoglobin level.
- Explain how pernicious anemia can cause a neurologic effect such as a tingling sensation in extremities or loss of coordination.
- Why is oral administration of vitamin B<sub>12</sub> not effective as a treatment for pernicious anemia?

### Aplastic Anemia

#### ■ Pathophysiology

Aplastic anemia results from impairment or failure of bone marrow, leading to loss of stem cells and **pancytopenia**, the decreased numbers of erythrocytes, leukocytes, and platelets in the blood. These deficits lead to many serious complications. In addition the bone



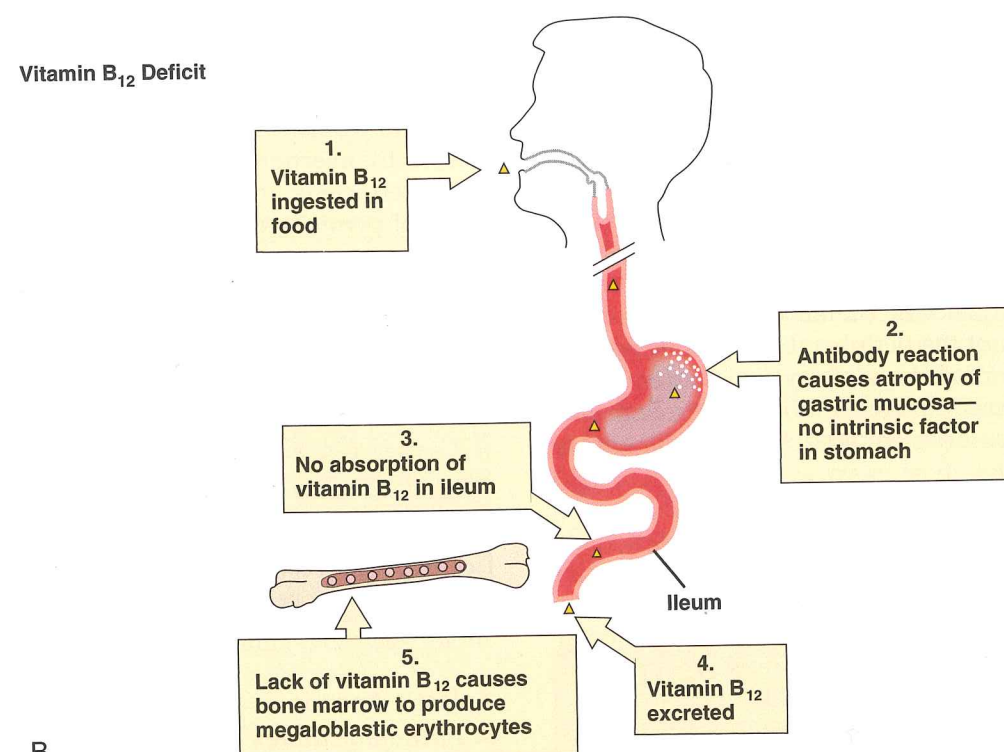
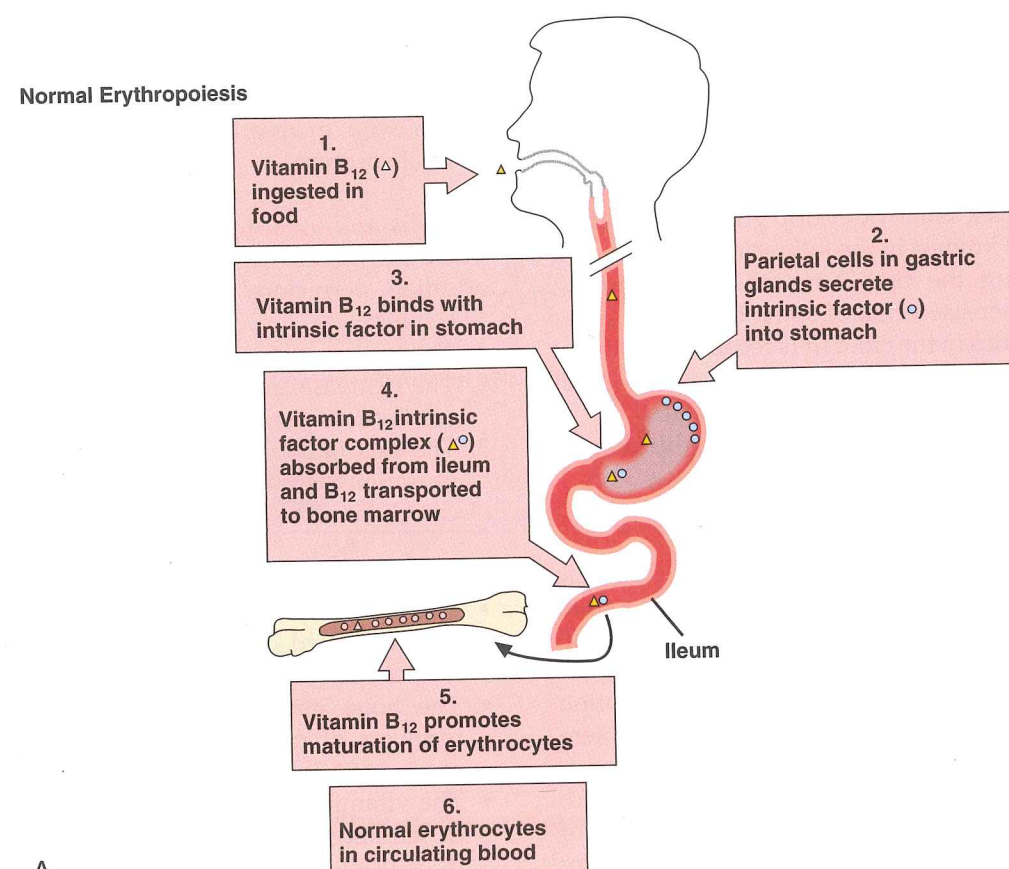
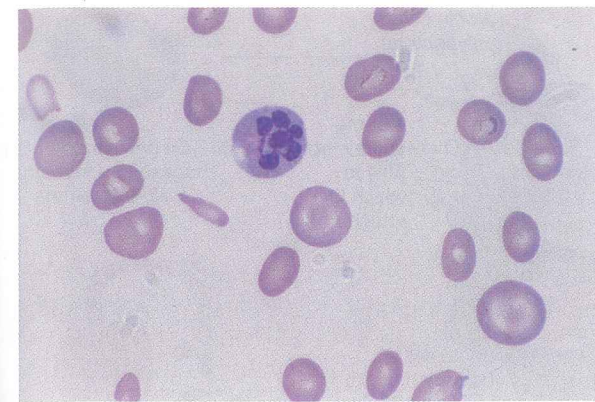


FIGURE 10-14 Development of pernicious anemia.

FIGURE 10-15 Vitamin B<sub>12</sub> deficiency with macrocytes and a neutrophil with hypersegmented nucleus in a peripheral blood smear. (From Stevens ML: Fundamentals of Clinical Hematology, Philadelphia, 1997, Saunders.)

marrow exhibits reduced cell components and increased fatty tissue.

### ■ Etiology

Aplastic anemia may be a temporary or permanent condition depending on the cause.

- In approximately half the cases, the patients are middle-aged, and the cause is unknown or idiopathic (primary type).
- **Myelotoxins**, such as radiation, industrial chemicals (e.g., benzene), and drugs (e.g., chloramphenicol, gold salts, phenylbutazone, phenytoin, and antineoplastic drugs) may damage the bone marrow. In these cases it is important to detect and remove the causative factor quickly to allow the marrow to recover. When severe aplastic anemia due to cancer treatment is a risk, the patient's stem cells may be harvested before treatment and then transfused later when needed.
- Viruses, particularly hepatitis C, may cause aplastic anemia.
- Autoimmune disease such as systemic lupus erythematosus (SLE) may affect the bone marrow.
- Genetic abnormalities such as **myelodysplastic** syndrome or Fanconi's anemia may also affect bone marrow function.

### ■ Signs and Symptoms

In the majority of cases, the onset is insidious. Because the entire bone marrow is affected, manifestations include those of:

1. Anemia (pallor, weakness, and dyspnea)
2. Leukopenia, such as recurrent or multiple infections
3. **Thrombocytopenia** (**petechiae**—flat, red, pinpoint hemorrhages on the skin [Fig. 10-19]—and a tendency to bleed excessively, particularly in the mouth) As blood counts diminish, particularly WBCs and platelets, uncontrollable infection and hemorrhage are likely.

### ■ Diagnostic Tests

Blood counts indicate pancytopenia. A bone marrow biopsy may be required to confirm the cause of the pancytopenia. The erythrocytes are often normal in appearance.

### ■ Treatment

Prompt treatment of the underlying cause and removal of any bone marrow suppressants are essential to recovery of the bone marrow. Blood transfusion may be necessary if stem cell levels are very low.

Bone marrow transplantation may be helpful in younger patients; its success depends on the accuracy of the tissue match using human leukocyte antigen (HLA). Chemotherapy and radiation are used to prepare the recipient's bone marrow for transplantation of stem cells (taken from the marrow of the pelvic bone of a suitable donor). Newer techniques allow harvesting of stem cells from the peripheral blood, not the marrow. The donor stem cells are infused intravenously into the blood of the recipient; they migrate to the bone marrow and provide a new source of blood cells after several weeks. Antirejection drugs are required for a year, but unlike the situation with other transplants, these drugs can then be discontinued. Common complications include damage to the digestive tract from the preparatory treatment, infection resulting from immune suppression, and rejection reactions.

### THINK ABOUT 10-5

- a. Explain why bone marrow damage can result in multiple, recurring infections.
- b. Explain why excessive bleeding occurs with aplastic anemia.
- c. Explain why it is necessary to treat the bone marrow recipient with chemotherapy and radiation before transplant.

### Hemolytic Anemias

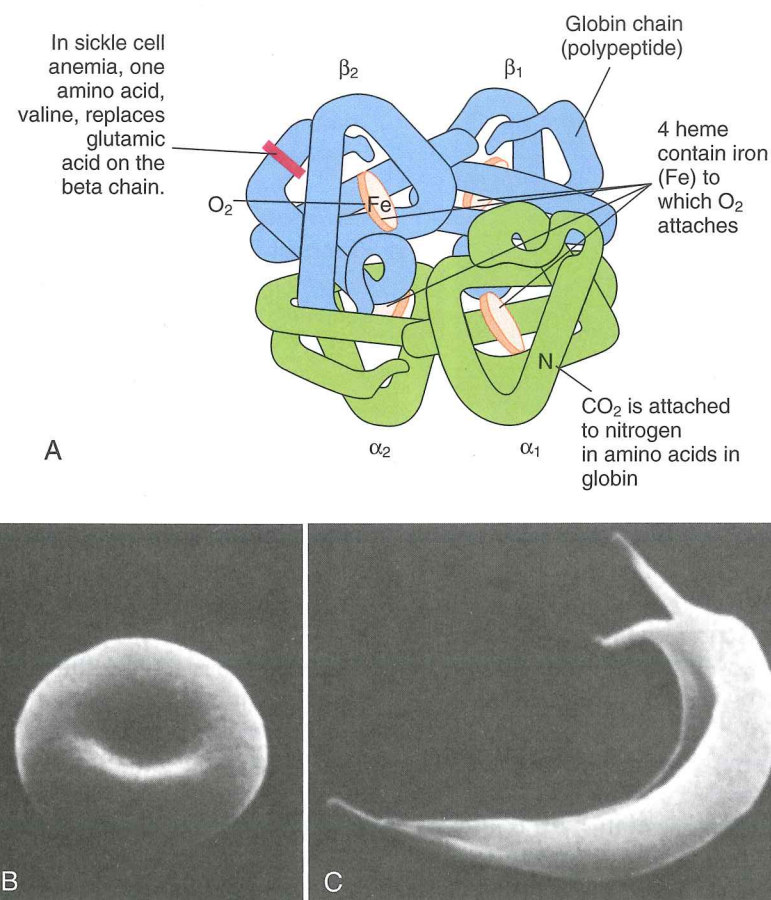
Hemolytic anemias result from excessive destruction of RBCs, or hemolysis, leading to a low erythrocyte count and low total hemoglobin. They have many causes, including genetic defects affecting structure, immune reactions, changes in blood chemistry, the presence of toxins in the blood, infections such as malaria, transfusion reactions, and blood incompatibility in the neonate (erythroblastosis fetalis). Two examples follow.

#### Sickle Cell Anemia

### ■ Pathophysiology

Sickle cell anemia is representative of a large number of similar hemoglobinopathies. In this anemia, an inherited characteristic leads to the formation of abnormal hemoglobin, hemoglobin S (HbS). In HbS, one amino





**FIGURE 10-16** A, Structure of hemoglobin. B, An oxygenated sickle cell erythrocyte. C, A deoxygenated sickle cell erythrocyte. (B and C courtesy of Dr. James White.)

acid in the pair of beta-globin chains has been changed from the normal glutamic acid to valine (Fig. 10-16). When this altered hemoglobin is deoxygenated, it crystallizes and changes the shape of the RBC from a disc to a crescent or "sickle" shape. The cell membrane is damaged, leading to hemolysis, and the cells have a much shorter lifespan than normal, perhaps only 20 days, instead of the normal 120 days. Initially the sickling may be reversible when increased oxygen is available, but after several episodes, the damage to the RBC is irreversible and hemolysis occurs. Hemoglobin S can transport oxygen in the normal fashion, but the erythrocyte count is very low, resulting in a low hemoglobin level in the blood.

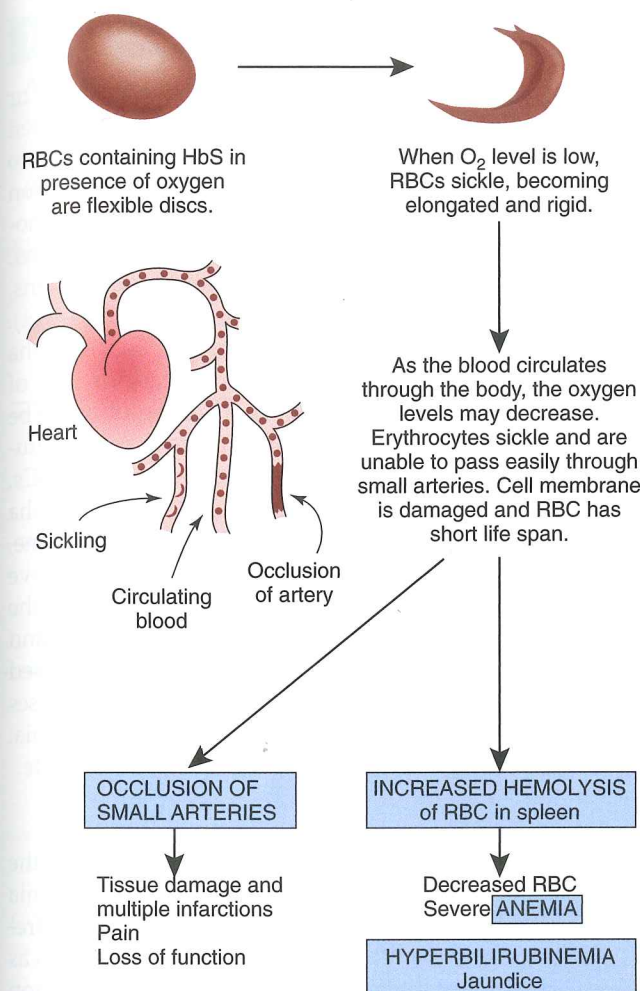
A major problem resulting from the sickling process is the obstruction of the small blood vessels by the elongated and rigid RBCs, resulting in thrombus formation and repeated multiple infarctions, or areas of tissue necrosis, throughout the body (Fig. 10-17). The deoxygenation of hemoglobin may occur in the peripheral circulation as the oxygen content of the blood is gradually reduced, leading to repeated minor infarctions. A serious crisis may occur in individuals with lung infection or dehydration when basic oxygen levels are reduced. During a sickling crisis, many larger blood

vessels may be involved, and multiple infarctions occur throughout the body, affecting the brain, bones, or organs. In time, significant damage and loss of function occur in many organ systems.

In addition to the basic anemia, the high rate of hemolysis leads to hyperbilirubinemia, jaundice, and gallstones (see Fig. 10-7 and Chapter 17).

### ■ Etiology

The gene for HbS is recessive and is very common in individuals from Africa and the Middle East. In homozygotes, most of the normal hemoglobin (hemoglobin A [HbA]) is replaced by HbS, resulting in clinical signs of sickle cell anemia (Fig. 10-18). Individuals vary greatly in the severity of the anemia and the number of sickling crises. In heterozygotes, less than half the hemoglobin is the abnormal HbS; therefore clinical signs occur only with severe hypoxia under unusual circumstances, for example, pneumonia or at high altitudes; this condition is termed the sickle cell trait. It is estimated that 1 in 12 African Americans have the trait and about 1 in 500 have sickle cell anemia. It is interesting that the carrier population in Africa is very high, evidently owing to a decreased incidence of malaria in those with HbS.



**FIGURE 10-17** Sickle cell anemia—the effects of sickling.

### ■ Signs and Symptoms

Clinical signs of sickle cell anemia do not appear until the child is about 12 months of age, when fetal hemoglobin (HbF) has been replaced by HbS. The proportion of HbS in the erythrocytes determines the severity of the condition.

- Severe anemia causes pallor, weakness, tachycardia, and dyspnea.
- Hyperbilirubinemia is indicated by jaundice, the yellowish color being most obvious in the sclerae of the eyes. The high bilirubin concentration in the bile may cause the development of gallstones (see Chapter 17).
- **Splenomegaly**, enlargement of the spleen, is common in young people because sickled cells cause congestion, but in adults the spleen is usually small and fibrotic owing to recurrent infarction.
- Vascular occlusions and infarctions lead to periodic painful crises and permanent damage to organs and tissues. Such damage may be manifested as ulcers on the legs and feet, areas of necrosis in the bones or kidneys, or seizures or hemiplegia resulting from cerebral infarctions (strokes). Pain can be quite intense.
- In the lungs, occlusions and infection cause acute chest syndrome with pain and fever. It can be diagnosed by x-ray. It is a frequent cause of death.
- Occlusions in the smaller blood vessels of the hands or feet cause hand-foot syndrome. Pain and swelling are often early signs in children.
- Growth and development are delayed. Late puberty is common. Tooth eruption is late, and hypoplasia is common. Intellectual development is usually impaired.

		PARENT WITH SICKLE CELL TRAIT		Probability
		s	a	
NORMAL PARENT	a	sa trait	aa normal	50% for child with sickle cell trait
	a	sa trait	aa normal	

A

		PARENT WITH SICKLE CELL TRAIT		Probability
		s	a	
PARENT WITH SICKLE CELL TRAIT	s	ss anemia	sa trait	25% normal 25% with sickle cell anemia 50% with sickle cell trait
	a	sa trait	aa normal	

B

		PARENT WITH SICKLE CELL ANEMIA		Probability
		s	s	
NORMAL PARENT	a	sa trait	sa trait	100% with sickle cell trait
	a	sa trait	sa trait	

C

KEY

aa = normal: HbA

ss = sickle cell anemia: HbS

sa = sickle cell trait: mixed HbA and HbS

**KEY**  
 aa = normal: HbA  
 ss = sickle cell anemia: HbS  
 sa = sickle cell trait: mixed HbA and HbS

**FIGURE 10-18** Inheritance of sickle cell anemia.



- Congestive heart failure may develop owing to constant efforts to improve the supply of oxygen and the increased peripheral resistance caused by the obstructions.
- Frequent infections occur because of the decreased defenses when the damaged spleen can no longer adequately filter the blood, the presence of necrotic tissues, and poor healing capabilities. Pneumonia is a common cause of death in children. Infections tend to cause more sickling, and a vicious cycle develops.

### ■ Diagnostic Tests

Carriers of the defective gene can be detected by a simple blood test (hemoglobin electrophoresis). This identification is useful in alerting those with sickle cell trait to avoid severe hypoxia and sickling episodes (e.g., with severe anemia, surgery, or at high altitudes), as well as in assisting prospective parents in decision making about the risk of having an affected child (see Chapter 21).

Prenatal diagnosis can be checked by DNA analysis of the fetal blood. In children more than 1 year of age, the diagnosis can be confirmed by the presence of sickled cells in peripheral blood and the presence of HbS. The bone marrow is hyperplastic, and more reticulocytes (immature RBCs) are released into the circulation.

### ■ Treatment

The search continues for more effective drugs to reduce sickling. The use of hydroxyurea (Hydrea) has reduced the frequency of crises and prolonged the lifespan for many, but is not effective for all patients. Dietary supplementation with folic acid (folate) is recommended even during asymptomatic periods. Avoidance of strenuous activity or high altitudes is helpful. Other supportive measures are utilized to prevent dehydration, acidosis, infection, or exposure to cold, all of which increase the sickling tendency and painful crises. Children should be immunized against pneumonia, influenza, and meningitis. Continued prophylactic penicillin may be necessary for two groups, young children and adults with severe cases. Gene therapy is under investigation. Bone marrow transplant is effective, but because of the limited number of African-American potential donors on bone marrow registries, it may be very difficult to find a match. In the past, patients rarely lived past their twenties, but recent improvements in care have extended the lifespan into middle age for many patients.

### THINK ABOUT 10-6

- Explain why vascular occlusions are common in patients with sickle cell disease.
- Compare sickle cell trait and sickle cell anemia in terms of the genetic factor involved, the amount of HbS present, and the presence of clinical signs.

### Thalassemia

#### ■ Pathophysiology

This anemia results from a genetic defect in which one or more genes for hemoglobin are missing or variant. When two genes are involved, thalassemia is moderate to severe. This abnormality interferes with the production of the globin chains, and therefore, the amount of hemoglobin synthesized and the number of RBCs is reduced. Hemoglobin is normally composed of four globin chains, two alpha and two beta (see structure in Fig. 10-16A). Thalassemia *alpha* refers to a reduction in or lack of alpha chains. Thalassemia *beta* refers to a decrease or lack of beta chains. In either case, less normal hemoglobin can be made. In addition to missing chains, there is an accumulation of the other available chains, damaging the RBCs. For example, when a beta chain is missing, the extra alpha chains collect in RBCs and damage the cell membrane, leading to hemolysis and anemia. Homozygotes have thalassemia major (Cooley's anemia) a severe form of the anemia; heterozygotes have thalassemia minor and exhibit mild signs of anemia. In severe cases, increased hemolysis of RBCs aggravates the anemia and causes splenomegaly, hepatomegaly, and hyperbilirubinemia. The bone marrow is hyperactive, trying to compensate.

### ■ Etiology

Thalassemia is the most common genetic disorder in the world and it occurs in two common forms. Thalassemia beta (autosomal dominant inheritance) occurs frequently in people from Mediterranean countries such as Greece or Italy, and thalassemia beta is the more common form. The alpha form is found in those of Indian, Chinese, or Southeast Asian descent. Because more than one gene is involved, there are many possible gene mutations with varied effects on hemoglobin synthesis and the severity of the resultant anemia.

### ■ Signs and Symptoms

The usual signs of anemia and increased hemolysis are present as described earlier. The child's growth and development are impaired directly by the hypoxia and indirectly by the fatigue and inactivity. Hyperactivity in the bone marrow leads to invasion of bone and impairs normal skeletal development. Heart failure develops as a result of the compensation mechanism increasing cardiac work load.

### ■ Diagnostic Tests

Red blood cells are microcytic, often varying in size, and hypochromic (low hemoglobin). There is an increase in erythropoietin levels. Often an iron overload exists. Prenatal diagnosis can be done by chorionic villus assay at 12 weeks or by amniocentesis at 16 weeks.

### ■ Treatment

Blood transfusions are the only treatment available at this time. Iron chelation therapy may be necessary to

TABLE 10-2 Comparison of Selected Anemias

Anemia	Characteristic RBC	Etiology	Additional Effects
Iron deficiency anemia	Microcytic, hypochromic Decreased hemoglobin production	Decreased dietary intake, malabsorption, blood loss	Only effects of anemia
Pernicious anemia	Megaloblasts (immature nucleated cells) Short lifespan	Deficit of intrinsic factor owing to immune reaction	Neurologic damage Achlorhydria
Aplastic anemia	Often normal cells Pancytopenia	Bone marrow damage or failure	Excessive bleeding and multiple infections
Sickle cell anemia	RBC elongates and hardens in "sickle" shape when O <sub>2</sub> levels are low—short lifespan	Recessive inheritance	Painful crises with multiple infarctions Hyperbilirubinemia



FIGURE 10-19 A, Facial ecchymoses. B, Petechiae. (From Young NS: Bone Marrow Failure Syndromes, Philadelphia, 2000, Saunders.)

remove the excess iron from numerous transfusions. Administration of folate is also recommended. Bone marrow transplants have been curative in some children and are in clinical research trials. Patients with mild forms of the disease have a normal lifespan, and those with moderate to severe disease live into their thirties with transfusions and chelation therapy. Those with very severe anemia may die in childhood.

Characteristics of the selected anemias are compared in Table 10-2.

### Blood-Clotting Disorders

Spontaneous bleeding or excessive bleeding following minor tissue trauma often indicates a blood-clotting disorder. Note: The following warning signs may also be caused by other factors, such as infections and damaged or fragile blood vessels (e.g., vitamin C deficit).

### WARNING SIGNS OF EXCESSIVE BLEEDING AND POSSIBLE BLOOD-CLOTTING DISORDERS

- Persistent bleeding from the gums (around the teeth) or repeated nosebleeds
- Petechiae—pinpoint flat red spots on skin or mucous membranes (like a rash); result from bleeding from a capillary or small arteriole (see Fig. 10-19B)
- Frequent purpura and ecchymoses—large, purplish red or greenish areas on the skin (bruises) (see Fig. 10-19A)
- More persistent bleeding than warranted by a trauma
- Bleeding into a joint—hemarthroses—swollen, red, and painful
- Coughing up blood—hemoptysis—bright red flecks in sputum
- Vomiting blood—hematemesis—often coarse brown particles (coffee grounds); may be red
- Blood in feces—often black (tarry) or occult (hidden)
- Anemia
- Feeling faint and anxious, low blood pressure, rapid pulse