As erythrocytes are destroyed within the reticuloendothelial system, free hemoglobin is ingested by macrophages and then split into heme and globin moieties. The heme ring is cleaved by the enzyme microsomal heme oxygenase to form biliverdin (*verde* = "green"), which is then converted to the tetrapyrol pigment bilirubin by the cytosolic enzyme biliverdin reductase. This unconjugated (or "indirect") bilirubin is released into the plasma, where it is tightly bound to albumin. Because unconjugated bilirubin is insoluble in water, it cannot be excreted in urine or bile. However, it is permeable across lipid-rich environments and therefore can traverse the blood-brain barrier and the placenta.

The unconjugated bilirubin-albumin complex is transported to the liver. Once in the space of Disse, this complex dissociates; unconjugated bilirubin is transported across the basolateral plasma membrane of liver cells and attaches to intracellular binding proteins (ligandins). It is then conjugated with glucuronic acid by the enzyme uridine diphosphate–glucuronyltransferase (UDP-GT) to form bilirubin monoglucuronide and diglucuronide, making the molecule water soluble. This conjugated (or "direct") bilirubin is excreted into bile via active transport across the canalicular membrane by means of a multispecific canalicular transport protein.

If biliary excretion of conjugated bilirubin is impaired, it can exit the basolateral membrane and reenter the circulation, causing an increase in plasma levels. Because conjugated bilirubin is water soluble and less tightly bound to albumin than its unconjugated form, it is readily filtered by the glomerulus and appears in the urine, giving it a dark color (choluria). Once in bile, bilirubin enters the intestine, where bacteria convert it to colorless tetrapyrroles (urobilinogens) that are excreted in feces. Up to 20% of urobilinogen is reabsorbed and undergoes enterohepatic circulation or excretion in urine.

LABORATORY MEASUREMENT OF BILIRUBIN

The *van den Bergh reaction,* which is the most commonly used test for detecting bilirubin in biologic fluids, combines bilirubin with diazotized sulfanilic acid to form a colored compound. The direct-reacting fraction is roughly equivalent to conjugated bilirubin and the indirect-reacting fraction (total minus direct fraction) to unconjugated bilirubin. This characteristic provides a means for classifying jaundice into two categories: unconjugated hyperbilirubinemia and conjugated hyperbilirubinemia.

UNCONJUGATED HYPERBILIRUBINEMIA

Mechanisms that cause unconjugated hyperbilirubinemia include overproduction, impaired hepatic uptake, and decreased conjugation of bilirubin. These disorders are not usually associated with significant hepatic disease.

Etiology of Hyperbilirubinemia

There are many potential causes of hyperbilirubinemia, and the major categories are summarized in Table 40-1. It is helpful to consider them mechanistically as conditions affecting the balance of bilirubin production, liver metabolism, and excretion. The classic cause of bilirubin overproduction is hemolysis, whereas the most common cause of impaired bilirubin uptake and metabolism is cirrhosis or other liver disease. Bile duct obstruction due to cancer, stones, or strictures is the most common cause of obstructive jaundice. Because multiple mechanisms are often involved in an individual patient, the evaluation of jaundice can be complex.

Prehepatic Jaundice

Prehepatic jaundice is associated with excessive bilirubin production (Fig. 40-1), which most often results from hemolysis (intravascular or extravascular), resolution of large hematomas, or mechanical injury to red cells, such as can occur with pulmonary emboli. Certain genetic diseases can lead to increased red cell lysis and therefore to hemolytic jaundice. Sickle cell anemia is the classic cause, but others include glucose 6-phosphate dehydrogenase deficiency and hereditary spherocytosis. Infectious diseases also can cause hemolysis, either directly (e.g., malaria) or indirectly (e.g., autoimmune injury). Jaundice resulting from hemolysis is characteristically mild in degree, and serum bilirubin levels rarely exceed 5 mg/dL in the absence of coexisting hepatic disease. Ineffective erythropoiesis, which may be significantly increased in megaloblastic anemias, also leads to mild jaundice.

Hemolysis should be considered in the evaluation of unconjugated hyperbilirubinemia and evaluated by examination of the peripheral blood smear (and, in some cases, the bone marrow

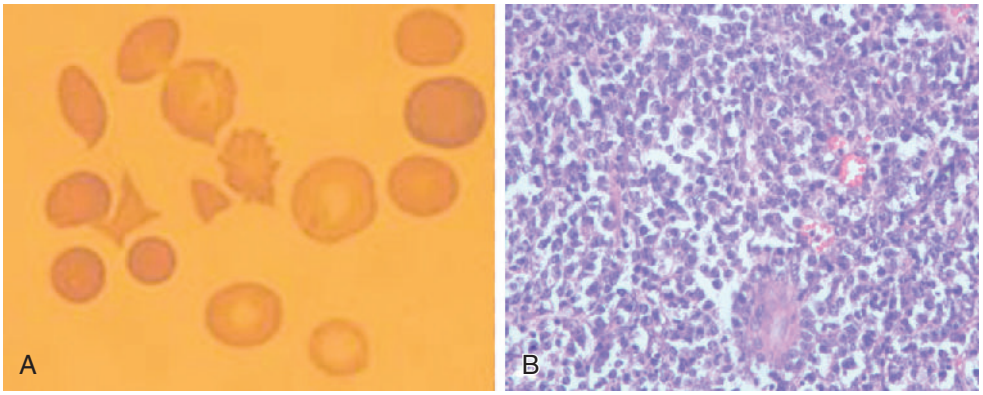

FIGURE 40-1 Hemolytic anemia associated with lymphoma. **A,** Blood smears show the destroyed red blood cells. **B,** Lymphoma.