In all types of uncomplicated hemolytic anemias, the excess serum bilirubin is unconjugated. The level of hyperbilirubinemia depends on the functional capacity of the liver and the rate of hemolysis. When the liver is normal, jaundice is rarely severe. Excessive bilirubin excreted by the liver into the gastrointestinal tract leads to increased formation and fecal excretion of urobilin (Chapter 18), and often leads to the formation of gallstones derived from heme pigments.

MORPHOLOGY

Certain changes are seen in hemolytic anemias regardless of cause or type. Anemia and lowered tissue oxygen tension trigger the production of erythropoietin, which stimulates erythroid differentiation and leads to the appearance of **increased numbers of erythroid precursors (normoblasts)** in the marrow (Fig. 14-1). Compensatory increases in erythropoiesis result in a **prominent reticulocytosis** in the peripheral blood. The phagocytosis of red cells leads to the accumulation of the iron containing pigment **hemosiderin**, particularly in the spleen, liver, and bone marrow. Such iron accumulation is referred to as **hemosiderosis**. If the anemia is severe, **extramedullary hematopoiesis** can appear in the liver, spleen, and lymph nodes. With chronic hemolysis, elevated biliary excretion of bilirubin promotes the formation of **pigment gallstones** (cholelithiasis).

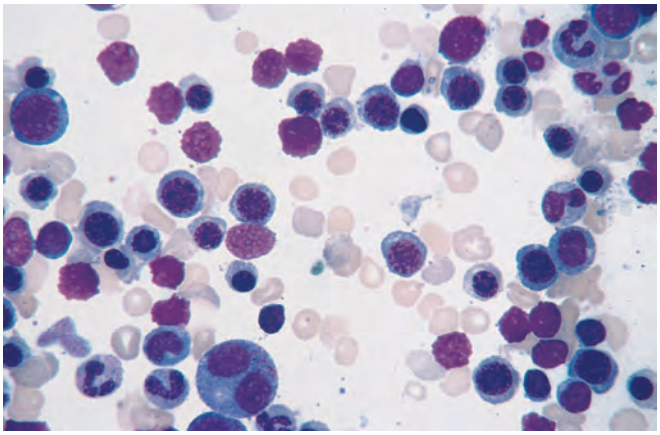

Figure 14-1 Marrow smear from a patient with hemolytic anemia. The marrow reveals increased numbers of maturing erythroid progenitors (normoblasts). (Courtesy Dr. Steven Kroft, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

The hemolytic anemias can be classified in a variety of ways; here, we rely on the underlying mechanisms (Table 14-1). We begin by discussing the major inherited forms of hemolytic anemia, and then move on to the acquired forms that are most common or of particular pathophysiologic interest.

Hereditary Spherocytosis

Hereditary spherocytosis (HS) is an inherited disorder caused by intrinsic defects in the red cell membrane skeleton that render red cells spheroid, less deformable, and vulnerable to splenic sequestration and destruction. The prevalence of HS is highest in northern Europe, where rates of 1 in 5000 are reported. An autosomal dominant inheritance pattern is seen in about 75% of cases. The remaining patients have a more severe form of the disease that is usually caused by the inheritance of two different defects (a state known as compound heterozygosity).

Pathogenesis. The remarkable deformability and durability of the normal red cell are attributable to the physicochemical properties of its specialized membrane skeleton (Fig. 14-2), which lies closely apposed to the internal surface of the plasma membrane. Its chief protein component, spectrin, consists of two polypeptide chains, α and β, which form intertwined (helical) flexible heterodimers. The "head" regions of spectrin dimers self-associate to form tetramers, while the "tails" associate with actin oligomers. Each actin oligomer can bind multiple spectrin tetramers, thus creating a two-dimensional spectrin-actin skeleton that is connected to the cell membrane by two distinct interactions. The first, involving the proteins ankyrin and band 4.2, binds spectrin to the transmembrane ion transporter, band 3. The second, involving protein 4.1, binds the "tail" of spectrin to another transmembrane protein, glycophorin A.

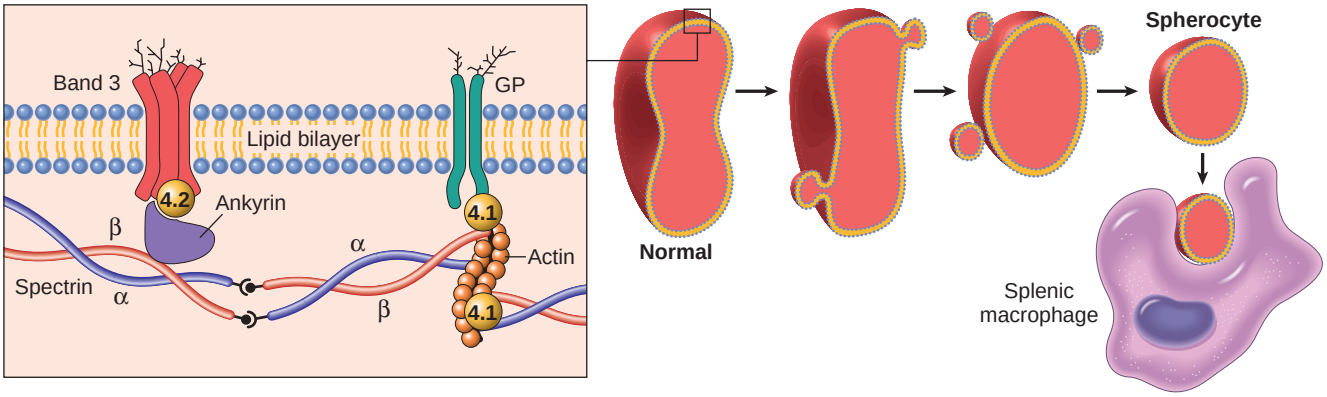

Figure 14-2 Role of the red cell membrane skeleton in hereditary spherocytosis. The left panel shows the normal organization of the major red cell membrane skeletal proteins. Various mutations involving α-spectrin, β-spectrin, ankyrin, band 4.2, or band 3 that weaken the interactions between these proteins cause red cells to lose membrane fragments. To accommodate the resultant change in the ratio of surface area to volume these cells adopt a spherical shape. Spherocytic cells are less deformable than normal ones and therefore become trapped in the splenic cords, where they are phagocytosed by macrophages. GP, Glycophorin.