HS is caused by diverse mutations that lead to an insufficiency of membrane skeletal components. As a result of these alterations, the life span of the affected red cells is decreased on average to 10 to 20 days from the normal 120 days. The pathogenic mutations most commonly affect ankyrin, band 3, spectrin, or band 4.2, the proteins involved in one of the two tethering interactions, presumably because this complex is particularly important in stabilizing the lipid bilayer. Most mutations cause frameshifts or introduce premature stop codons, such that the mutated allele fails to produce any protein. The resulting deficiency of the affected protein reduces the assembly of the skeleton as a whole, destabilizing the overlying plasma membrane. Young HS red cells are normal in shape, but the destabilized lipid bilayer sheds membrane fragments as red cells age in the circulation. The loss of membrane relative to cytoplasm "forces" the cells to assume the smallest possible diameter for a given volume, namely, a sphere. Compound heterozygosity for two defective alleles understandably results in a more severe membrane skeleton deficiency.

The invariably beneficial effects of splenectomy prove that the spleen has a cardinal role in the premature demise of spherocytes. The travails of spherocytic red cells are fairly well defined. In the life of the portly inflexible spherocyte, the spleen is the villain. Normal red cells must undergo extreme deformation to leave the cords of Billroth and enter the sinusoids. Because of their spheroidal shape and reduced deformability, the hapless spherocytes are trapped in the splenic cords, where they are easy prey for macrophages. The splenic environment also somehow exacerbates the tendency of HS red cells to lose membrane along with K^+ ions and H_2O; prolonged splenic exposure (erythrostasis), depletion of red cell glucose, and diminished red cell pH have all been suggested to contribute to these abnormalities (Fig. 14-3). After splenectomy the spherocytes persist, but the anemia is corrected.

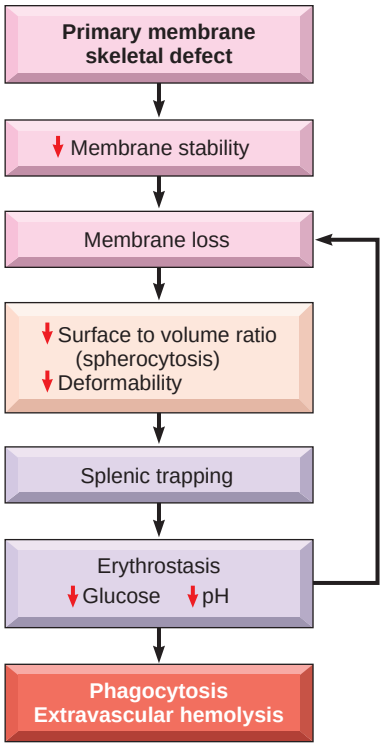

Figure 14-3 Pathophysiology of hereditary spherocytosis.

MORPHOLOGY

The most specific morphologic finding is **spherocytosis**, apparent on smears as small, dark-staining (hyperchromic) red cells lacking the central zone of pallor (Fig. 14-4). Spherocytosis is distinctive but not pathognomonic, as spherocytes are also seen in other disorders associated with membrane loss, such as in autoimmune hemolytic anemia. Other features are common to all hemolytic anemias. These include reticulocytosis, marrow erythroid hyperplasia, hemosiderosis, and mild jaundice. **Cholelithiasis** (pigment stones) occurs in 40% to 50% of affected adults. Moderate **splenomegaly** is characteristic (500-1000 gm); in few other hemolytic anemias is the spleen enlarged as much or as consistently. Splenomegaly results from congestion of the cords of Billroth and increased numbers of phagocytes.

Clinical Features. The diagnosis is based on family history, hematologic findings, and laboratory evidence. In two thirds of the patients the red cells are abnormally sensitive to *osmotic lysis* when incubated in hypotonic salt solutions, which causes the influx of water into spherocytes with little margin for expansion. HS red cells also have an *increased mean cell hemoglobin concentration*, due to dehydration caused by the loss of K^+ and H_2O.

The characteristic clinical features are *anemia, splenomegaly, and jaundice*. The severity varies greatly. In a small minority (mainly compound heterozygotes) HS presents at birth with marked jaundice and requires exchange transfusions. In 20% to 30% of patients the disease is so mild as to be virtually asymptomatic; here the decreased red cell survival is readily compensated for by increased erythropoiesis. In most, however, the compensatory changes are outpaced, producing a chronic hemolytic anemia of mild to moderate severity.

The generally stable clinical course is sometimes punctuated by *aplastic crises,* usually triggered by an acute parvovirus infection. Parvovirus infects and kills red cell

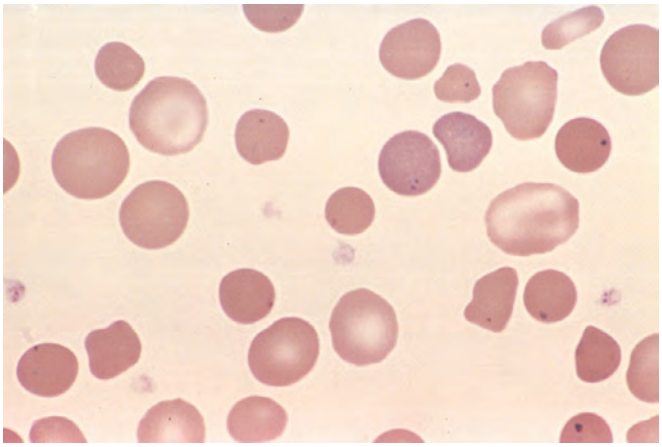

Figure 14-4 Hereditary spherocytosis (peripheral smear). Note the anisocytosis and several dark-appearing spherocytes with no central pallor. Howell-Jolly bodies (small dark nuclear remnants) are also present in red cells of this asplenic patient. (Courtesy Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)