



Figure 14-6 Glucose-6-phosphate dehydrogenase deficiency: effects of oxidant drug exposure (peripheral blood smear). *Inset*, Red cells with precipitates of denatured globin (Heinz bodies) revealed by supravital staining. As the splenic macrophages pluck out these inclusions, “bite cells” like the one in this smear are produced. (Courtesy Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

continues to take the offending drug). The recovery phase is heralded by reticulocytosis. Because hemolytic episodes related to G6PD deficiency occur intermittently, features related to chronic hemolysis (e.g., splenomegaly, cholelithiasis) are absent.

Sickle Cell Disease

Sickle cell disease is a common hereditary hemoglobinopathy caused by a point mutation in β -globin that promotes the polymerization of deoxygenated hemoglobin, leading to red cell distortion, hemolytic anemia, microvascular obstruction, and ischemic tissue damage. Several hundred different hemoglobinopathies caused by mutations in globin genes are known, but only those associated with sickle cell disease are prevalent enough in the United States to merit discussion. Hemoglobin is a tetrameric protein composed of two pairs of globin chains, each with its own heme group. Normal adult red cells contain mainly HbA ($\alpha_2\beta_2$), along with small amounts of HbA₂ ($\alpha_2\delta_2$) and fetal hemoglobin (HbF; $\alpha_2\gamma_2$). Sickle cell disease is caused by a point mutation in the sixth codon of β -globin that leads to the replacement of a glutamate residue with a valine residue. The abnormal physiochemical properties of the resulting sickle hemoglobin (HbS) are responsible for the disease.

About 8% to 10% of African Americans, or roughly 2 million individuals, are heterozygous for HbS, a largely asymptomatic condition known as sickle cell trait. The offspring of two heterozygotes has a 1 in 4 chance of being homozygous for the sickle mutation, a state that produces symptomatic sickle cell disease. In such individuals, almost all the hemoglobin in the red cell is HbS ($\alpha_2\beta^S_2$). There are about 70,000 individuals with sickle cell disease in the United States. In certain populations in Africa the prevalence of heterozygosity is as high as 30%.

This high frequency stems from protection afforded by HbS against falciparum malaria. Population studies have shown that the sickle hemoglobin mutation has arisen independently at least six times in areas in which falciparum

malaria is endemic, providing clear evidence of strong Darwinian selection for this trait. Parasite densities are lower in infected AS children than in AA children, and AS children are significantly less likely to have severe disease or to die from malaria. While mechanistic details are lacking two scenarios to explain these observations are favored:

- Metabolically active intracellular parasites consume O₂ and decrease intracellular pH, both of which promote hemoglobin sickling in AS red cells. These distorted and stiffened cells may be cleared more rapidly by phagocytes in the spleen and liver, helping to keep parasite loads down.
- Another effect of sickling is that it impairs the formation of membrane knobs containing a protein made by the parasite called PfEMP-1. These membrane knobs are implicated in adhesion of infected red cells to endothelium, which is believed to have an important pathogenic role in the most severe form of the disease, cerebral malaria.

It has been suggested that G6PD deficiency and thalassemias also protect against malaria by increasing the clearance and decreasing the adherence of infected red cells, possibly by raised levels of oxidant stress and causing membrane damage in the parasite-bearing cells.

Pathogenesis. The major pathologic manifestations—chronic hemolysis, microvascular occlusions, and tissue damage—all stem from the tendency of HbS molecules to stack into polymers when deoxygenated. Initially, this process converts the red cell cytosol from a freely flowing liquid into a viscous gel. With continued deoxygenation HbS molecules assemble into long needle-like fibers within red cells, producing a distorted sickle or holly-leaf shape.

Several variables affect the rate and degree of sickling:

- *Interaction of HbS with the other types of hemoglobin in the cell.* In heterozygotes with sickle cell trait, about 40% of the hemoglobin is HbS and the rest is HbA, which interferes with HbS polymerization. As a result, red cells in heterozygous individuals do not sickle except under conditions of profound hypoxia. HbF inhibits the polymerization of HbS even more than HbA; hence, infants do not become symptomatic until they reach 5 or 6 months of age, when the level of HbF normally falls. However, in some individuals HbF expression remains at relatively high levels, a condition known as hereditary persistence of HbF; in these individuals, sickle cell disease is much less severe. Another variant hemoglobin is HbC, in which lysine is substituted for glutamate in the sixth amino acid residue of β -globin. HbC is also common in regions where HbS is found; overall, about 2% to 3% of American blacks are HbC heterozygotes and about 1 in 1250 are compound HbS/HbC heterozygotes. In HbSC red cells the percentage of HbS is 50%, as compared with only 40% in HbAS cells. Moreover, HbSC cells tend to lose salt and water and become dehydrated, which increases the intracellular concentration of HbS. Both of these factors increase the tendency for HbS to polymerize. As a result, individuals who are compound heterozygotes for HbS and HbC have a symptomatic sickling disorder (termed *HbSC disease*), but it is milder than sickle cell disease.