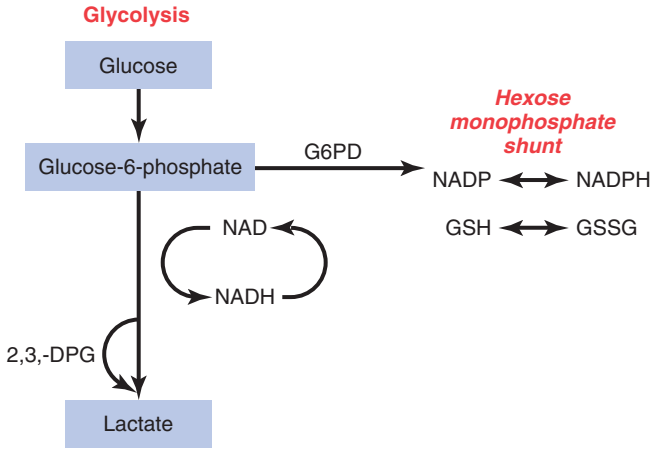

FIGURE 47-4 Metabolism of the red blood cell. 2,3-DPG, 2,3-Diphosphoglycerate; G6PD, glucose-6-phosphate dehydrogenase; GSH, reduced glutathione; GSSG, reduced and oxidized glutathione; NAD, nicotinamide adenine dinucleotide; NADH, reduced form of NAD; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, reduced form of NADP.

The African form of G6PD deficiency is relatively mild, whereas the Mediterranean form is severe.

Absence of G6PD renders erythrocytes sensitive to oxidative stress. In the setting of infection, acidosis, or oxidant drugs, hemoglobin may precipitate within the cells, causing hemolysis. Many drugs are associated with hemolysis in the setting of G6PD deficiency, including sulfonamides, antimalarials, dapsone, aspirin, and phenacetin. The diagnosis should be considered in male patients of African American or Mediterranean extraction who have evidence of hemolysis in the setting of acute infection or recent exposure to oxidant drugs. Patients with the Mediterranean variant of G6PD deficiency may develop hemolysis on exposure to fava beans (favism). Cells with precipitated hemoglobin contain Heinz bodies that can be visualized with crystal violet staining of the peripheral blood smear. These inclusions are removed in the spleen, resulting in the additional finding of bite cells in the blood smear. The diagnosis can be confirmed with measurement of G6PD levels in the peripheral blood. However, reticulocytes and young RBCs in patients with G6PD deficiency have a higher enzyme level; consequently, if the diagnosis is probable, the patients with a normal G6PD level should be retested at a time removed from the acute episode, when the percentage of young RBCs is high. The mainstay of preventing hemolysis in these patients is avoidance of oxidative stress, especially drugs implicated in causing hemolysis. Splenectomy is recommended only for patients with severe episodic or chronic hemolysis.

Other Enzyme Deficiencies

Enzyme deficiencies as rare causes of hemolytic anemia have been reported involving almost all of the enzymes of the glycolytic pathway. The most common of these is pyruvate kinase deficiency. Autosomal genes encode these enzymes, and the pattern of inheritance is therefore autosomal recessive.

More information on hemolytic anemias caused by inherited enzyme deficiencies can be found in Chapter 161, "Hemolytic Anemias: Red Cell Membrane and Metabolic Defects," in Goldman-Cecil Medicine, *25th Edition.*

TABLE 47-8 CLINICAL MANIFESTATIONS OF SICKLE CELL DISEASE

ACUTE MANIFESTATIONS	CHRONIC MANIFESTATIONS
Vaso-occlusive crisis	Chronic renal disease
Painful crisis	Isosthenuria
Acute chest syndrome	Chronic renal failure
Priapism	Chronic pulmonary disease
Cerebrovascular events	Sickle hepatopathy
Thrombotic stroke	Proliferative retinopathy
Hemorrhagic stroke	Avascular necrosis
Aplastic crisis	Skin ulcers
Splenic sequestration	
Osteomyelitis	

Hemoglobinopathies

Hemoglobinopathies are disorders caused by mutations that result in the synthesis of quantitatively or qualitatively abnormal hemoglobins. The most common of these are the sickle syndromes and the thalassemias, which, like G6PD deficiency, arose in areas of the world with endemic malaria.

Sickle Cell Disease

Sickle cell disease, the most common of the sickle syndromes, arises from a point mutation that causes a substitution of valine for glutamic acid in the sixth amino acid of the β-globin gene. It has arisen as an independent mutation in diverse populations in Africa, India, the Mediterranean, and the Middle East. The substitution of a hydrophobic for a hydrophilic residue renders the deoxygenated sickle hemoglobin (HbS) less soluble and therefore susceptible to polymerization and precipitation. The rate of precipitation of HbS is exquisitely sensitive to the intracorpuscular concentration of deoxygenated hemoglobin. Sickling is therefore increased in settings in which that concentration is increased, either by changes in cellular hydration (dehydration) or by changes in the oxygen dissociation curve (e.g., hypoxia, acidosis, high altitude).

Acute Manifestations

Most of the acute complications of sickle cell disease are related to vaso-occlusion (Table 47-8). Painful crises, secondary to occlusions of the microvasculature and ischemia of organs and tissues, can occur anywhere, with pain most commonly experienced in the extremities, chest, abdomen, and back. Painful crises are commonly precipitated by infections, dehydration, rapid changes in temperature, and pregnancy. Often, however, no obvious precipitating cause is found for an acute painful crisis.

Vaso-occlusion in the pulmonary circulation can be a particularly ominous complication of sickle cell disease. It results in the *acute chest syndrome*, which is characterized by chest pain, hypoxemia, and pulmonary infiltrates. The roles of infection, infarction, and in situ thrombosis in the acute chest syndrome are indistinguishable, but all patients should receive antibiotics for presumed pneumonia. Because hypoxemia predisposes to further sickling and increasing respiratory compromise, the acute chest syndrome is life-threatening and is an indication for emergent exchange transfusion.