SPECIAL INTEREST BOX 10.2 Glucose-6-Phosphate Dehydrogenase Deficiency

Because of their role in oxygen transport, red blood cells are especially prone to oxidative stress. The millions of hemoglobin molecules within each cell are potential prooxidants, that is, the heme group promotes the production of ROS. Recall that oxygen attaches to the sixth coordination bond of the heme group (see p. 145):

$$[Fe^{2+}(\text{heme})(\text{His})(O_2)]$$

When it does so, an intermediate structure forms in which an electron is delocalized between the iron atom and the oxygen:

$$[Fe^{2+}(O_2)] \rightleftharpoons [Fe^{3}(O_2^{-})]$$

Occasionally, oxyhemoglobin decomposes and releases O_2^-. Under normal conditions, a few percent of hemoglobin molecules become oxidized at any one time. Consequently, red blood cells are constantly exposed to O_2^- and the oxidized product of hemoglobin, called methemoglobin, with its heme- Fe^{3+} group is no longer able to bind oxygen. Red blood cells become fragile because the lipid peroxidation caused by H_2O_2 damages the cell's plasma membrane. When such cells pass through narrow blood vessels, they may rupture. If the oxidative stress is severe, hemolytic anemia results. Fortunately, red blood cells are usually well protected. They possess high concentrations of Cu-Zn SOD, catalase, and glutathione peroxidase, and a very active pentose phosphate pathway. The NADPH produced by the oxidative phase of the pentose phosphate pathway is used to reduce GSSG to GSH (Figure 10.21). However, red blood cells have a specific vulnerability to oxidative stress because they derive NADPH only from the pentose phosphate pathway.

In *glucose-6-phosphate dehydrogenase deficiency*, the red blood cell's capacity to protect itself from oxidative stress is reduced. Affected individuals produce low amounts of NADPH because they possess a defective enzyme. (There are over 100 known variants of the G-6-PD gene. The capacity to produce NADPH therefore varies widely among G-6-PD–deficient individuals.) A lower than normal NADPH concentration impairs the individual's capacity to generate GSH.

Under normal conditions, many carriers of the mutant gene are asymptomatic. However, any additional oxidative stress can have serious consequences. For example, administration of the antimalarial drug primaquine to G-6-PD–deficient individuals results in hemolytic anemia. The drug kills the malarial parasite *Plasmodium* because it stimulates the production of hydrogen peroxide. The resultant lowering of NADPH and GSH levels in red blood cells (that already have lower than normal amounts) causes the lysis of the red cell membrane. G-6-PD–deficient individuals are resistant to malaria. (*Plasmodium* is especially sensitive to oxidizing conditions, so any circumstance that lowers cellular antioxidant capacity inhibits the infection.) It is not surprising, therefore, that G-6-PD deficiency is one of the most common human genetic anomalies. In geographic areas in which malaria is endemic (e.g., the Mediterranean and Middle East regions), individuals who possess the defective enzyme are less likely to die of the disease than those who do not. (Recall that sickle-cell trait also confers resistance to malaria.)