progenitors, effectively causing red cell production to cease until an immune response commences, generally in 1 to 2 weeks. Because of the reduced life span of HS red cells, cessation of erythropoiesis for even short time periods leads to sudden worsening of the anemia. Transfusions may be necessary to support the patient until the immune response clears the infection. *Hemolytic crises* are produced by intercurrent events leading to increased splenic destruction of red cells (e.g., infectious mononucleosis); these are clinically less significant than aplastic crises. Gallstones, found in many patients, can also produce symptoms. Splenectomy treats the anemia and its complications, but brings with it an increased risk of sepsis, since the spleen acts as an important filter for blood borne bacteria.

Hemolytic Disease Due to Red Cell Enzyme Defects: Glucose-6-Phosphate Dehydrogenase Deficiency

Abnormalities in the hexose monophosphate shunt or glutathione metabolism resulting from deficient or impaired enzyme function reduce the ability of red cells to protect themselves against oxidative injuries and lead to hemolysis. The most important of these enzyme derangements is the hereditary deficiency of glucose-6-phosphate dehydrogenase (G6PD) activity. G6PD reduces nicotinamide adenine dinucleotide phosphate (NADP) to NADPH while oxidizing glucose-6-phosphate (Fig. 14-5). NADPH then provides reducing equivalents needed for conversion of oxidized glutathione to reduced glutathione, which protects against oxidant injury by participating as a cofactor in reactions that neutralize compounds such as H_2O_2 (Fig. 14-5).

G6PD deficiency is a recessive X-linked trait, placing males at higher risk for symptomatic disease. Several hundred G6PD genetic variants are known, but most

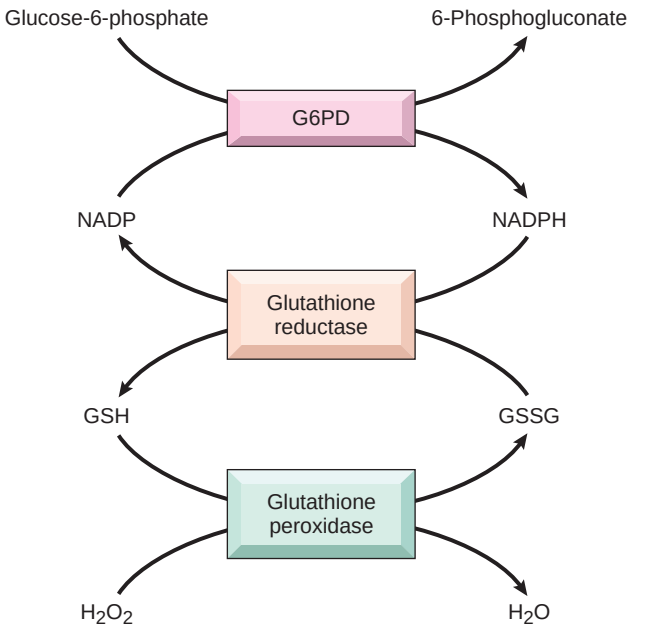

Figure 14-5 Role of glucose-6-phosphate dehydrogenase (G6PD) in defense against oxidant injury. The disposal of H_2O_2, a potential oxidant, is dependent on the adequacy of reduced glutathione (GSH), which is generated by the action of the reduced form of nicotinamide adenine dinucleotide (NADPH). The synthesis of NADPH is dependent on the activity of G6PD. GSSG, Oxidized glutathione.

are harmless. Two variants, designated G6PD$^-$ and G6PD Mediterranean, cause most of the clinically significant hemolytic anemias. G6PD$^-$ is present in about 10% of American blacks; G6PD Mediterranean, as the name implies, is prevalent in the Middle East. The high frequency of these variants in each population is believed to stem from a protective effect against *Plasmodium falciparum* malaria (discussed later). G6PD variants associated with hemolysis result in misfolding of the protein, making it more susceptible to proteolytic degradation. Compared with the most common normal variant, G6PD B, the half-life of G6PD$^-$ is moderately reduced, whereas that of G6PD Mediterranean is more markedly abnormal. Because mature red cells do not synthesize new proteins, G6PD$^-$ or G6PD Mediterranean enzyme activities fall quickly to levels inadequate to protect against oxidant stress as red cells age. Thus, older red cells are much more prone to hemolysis than younger ones.

The episodic hemolysis that is characteristic of G6PD deficiency is caused by exposures that generate oxidant stress. The most common triggers are *infections*, in which oxygen-derived free radicals are produced by activated leukocytes. Many infections can trigger hemolysis; viral hepatitis, pneumonia, and typhoid fever are among those most likely to do so. The other important initiators are *drugs* and certain *foods.* The oxidant drugs implicated are numerous, including antimalarials (e.g., primaquine and chloroquine), sulfonamides, nitrofurantoins, and others. Some drugs cause hemolysis only in individuals with the more severe Mediterranean variant. The most frequently cited food is the *fava bean,* which generates oxidants when metabolized. "Favism" is endemic in the Mediterranean, Middle East, and parts of Africa where consumption is prevalent. Uncommonly, G6PD deficiency presents as neonatal jaundice or a chronic low-grade hemolytic anemia in the absence of infection or known environmental triggers.

Oxidants cause both *intravascular and extravascular hemolysis* in G6PD-deficient individuals. Exposure of G6PD-deficient red cells to high levels of oxidants causes the cross-linking of reactive sulfhydryl groups on globin chains, which become denatured and form membrane-bound precipitates known as *Heinz bodies.* These are seen as dark inclusions within red cells stained with crystal violet (Fig. 14-6). Heinz bodies can damage the membrane sufficiently to cause intravascular hemolysis. Less severe membrane damage results in decreased red cell deformability. As inclusion-bearing red cells pass through the splenic cords, macrophages pluck out the Heinz bodies. As a result of membrane damage, some of these partially devoured cells retain an abnormal shape, appearing to have a bite taken out of them (Fig. 14-6). Other less severely damaged cells become spherocytes due to loss of membrane surface area. Both bite cells and spherocytes are trapped in splenic cords and removed rapidly by phagocytes.

Acute intravascular hemolysis, marked by anemia, hemoglobinemia, and hemoglobinuria, usually begins 2 to 3 days following exposure of G6PD-deficient individuals to oxidants. The hemolysis is greater in individuals with the highly unstable G6PD Mediterranean variant. Because only older red cells are at risk for lysis, the episode is self-limited, as hemolysis ceases when only younger G6PD-replete red cells remain (even if the patient

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