an intracorpuscular cause and an extracorpuscular cause, because in the majority of cases hemolysis is triggered by an exogenous agent. Although a decrease in G6PD activity is present in most tissues of G6PD-deficient subjects, in other cells, the decrease is much less marked than in red cells, and it does not seem to impact on clinical expression.

GENETIC CONSIDERATIONS

The *G6PD* gene is X-linked, and this has important implications. First, because males have only one *G6PD* gene (i.e., they are hemizygous for this gene), they must be either normal or G6PD deficient. By contrast, females, who have two *G6PD* genes, can be either normal or deficient (homozygous) or intermediate (heterozygous). As a result of the phenomenon of X chromosome inactivation, heterozygous females are genetic mosaics, with a highly variable ratio of G6PD-normal to G6PD-deficient cells and an equally variable degree of clinical expression; some heterozygotes can be just as affected as hemizygous males. The enzymatically active form of G6PD is either a dimer or a tetramer of a single protein subunit of 514 amino acids. G6PD-deficient subjects have been found invariably to have mutations in the coding region of the *G6PD* gene (Fig. 129-5). Almost all of the approximately 180 different mutations known are single missense point mutations, entailing single amino acid replacements in the G6PD protein. In most cases, these mutations cause G6PD deficiency by decreasing the in vivo stability of the protein; thus, the physiologic decrease in G6PD activity that takes place with red cell aging is greatly accelerated. In some cases, an amino acid replacement can also affect the catalytic function of the enzyme.

Among these mutations, those underlying chronic nonspherocytic hemolytic anemia (CNSHA; see below) are a discrete subset. This much more severe clinical phenotype can be ascribed in some cases to adverse qualitative changes (for instance, a decreased affinity for the substrate, glucose 6-phosphate) or simply to the fact that the enzyme deficit is more extreme, because of a more severe instability of the enzyme. For instance, a cluster of mutations map at or near the dimer interface, and clearly they compromise severely the formation of the dimer.

Epidemiology G6PD deficiency is widely distributed in tropical and subtropical parts of the world (Africa, Southern Europe, the Middle East, Southeast Asia, and Oceania) **(Fig. 129-6)** and wherever people from those areas have migrated. A conservative estimate is that at least 400 million people have a *G6PD* deficiency gene. In several of these areas, the frequency of a *G6PD* deficiency gene may be as high as 20% or more. It would be quite extraordinary for a trait that causes significant pathology to spread widely and reach high frequencies in many populations without conferring some biologic advantage. Indeed, G6PD is one of the best-characterized examples of genetic polymorphisms in the human species. Clinical field studies and in vitro experiments strongly support the view that G6PD deficiency has been selected by *Plasmodium falciparum* malaria, by virtue of the fact that it confers a relative resistance against this highly lethal infection. Different G6PD variants underlie G6PD deficiency in different parts of the world. Some of the more widespread variants are G6PD Mediterranean on the shores of that sea, in the Middle East, and in India; G6PD A– in Africa and in Southern Europe; G6PD Vianchan and G6PD Mahidol in Southeast Asia; G6PD Canton in China; and G6PD Union worldwide. The heterogeneity of polymorphic G6PD variants is proof of their independent origin, and it supports the notion that they have been selected by a common environmental agent, in keeping with the concept of convergent evolution (Fig. 129-6).

Clinical manifestations The vast majority of people with G6PD deficiency remain clinically asymptomatic throughout their lifetime; however, all of them have an increased risk of developing neonatal jaundice (NNJ) and a risk of developing acute HA (AHA) when challenged by a number of oxidative agents. NNJ related to G6PD deficiency is very rarely present at birth; the peak incidence of clinical onset is between day 2 and day 3, and in most cases, the anemia is not severe. However, NNJ can be very severe in some G6PD-deficient babies, especially in association with prematurity, infection, and/or environmental factors (such as naphthalene-camphor balls, which are used in babies' bedding and clothing), and the risk of severe NNJ is also increased by the coexistence of a monoallelic or biallelic mutation in the uridyl transferase gene (*UGT1A1*; the same mutations are associated with Gilbert's syndrome). If inadequately managed, NNJ associated with G6PD deficiency can produce kernicterus and permanent neurologic damage.

AHA can develop as a result of three types of triggers: (1) fava beans, (2) infections, and (3) drugs **(Table 129-5)**. Typically, a hemolytic attack starts with malaise, weakness, and abdominal or lumbar pain. After an interval of several hours to 2–3 days, the patient develops jaundice and often dark urine. The onset can be extremely abrupt, especially with favism in children. The anemia is moderate to extremely severe, usually normocytic and normochromic, and due partly to intravascular hemolysis; hence, it is associated with hemoglobinemia, hemoglobinuria, high LDH, and low or absent plasma haptoglobin. The blood film shows anisocytosis, polychromasia, and spherocytes typical of hemolytic anemias. The most typical feature of G6PD deficiency is the presence of bizarre poikilocytes, with red cells that appear to have unevenly distributed hemoglobin ("hemighosts") and red cells that appear to have had parts of them bitten away ("bite cells" or "blister cells") **(Fig. 129-7)**. A classical test, now rarely carried out, is supravital staining with methyl violet, which, if done promptly, reveals the presence of Heinz bodies (consisting of precipitates of denatured hemoglobin and hemichromes), which are regarded as a signature of oxidative damage to red cells (they are also seen with unstable hemoglobins). LDH is high, and so is the unconjugated

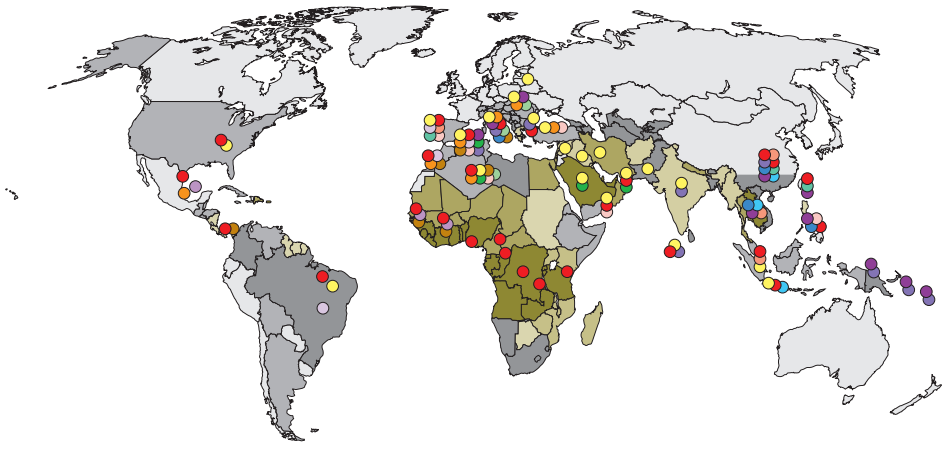

FIGURE 129-6 Epidemiology of glucose 6-phosphate dehydrogenase (G6PD) deficiency throughout the world. The different shadings indicate increasingly high levels of prevalence, up to about 20%; the different colored symbols indicate individual genetic variants of G6PD, each one having a different mutation. *(From L Luzzatto et al, in C Scriver et al [eds]: The Metabolic & Molecular Bases of Inherited Disease, 8th ed. New York, McGraw-Hill, 2001.)*