TABLE 129-4 RED CELL ENZYME ABNORMALITIES CAUSING HEMOLYSIS

	Enzyme (Acronym)	Chromosomal Location	Prevalence of Enzyme Deficiency (Rank)	Clinical Manifestations Extra-Red Cell	Comments
Glycolytic Pathway					
	Hexokinase (HK)	10q22	Very rare		Other isoenzymes known
	Glucose 6-phosphate isomerase (G6PI)	19q31.1	Rare (4)[a]	NM, CNS	
	Phosphofructokinase (PFK)	12q13	Very rare	Myopathy	
	Aldolase	16q22-24	Very rare		
	Triose phosphate isomerase (TPI)	12p13	Very rare	CNS (severe), NM	
	Glyceraldehyde 3-phosphate dehydrogenase (GAPD)	12p13.31-p13.1	Very rare	Myopathy	
	Diphosphoglycerate mutase (DPGM)	7q31-q34	Very rare		Erythrocytosis rather than hemolysis
	Phosphoglycerate kinase (PGK)	Xq13	Very rare	CNS, NM	May benefit from splenectomy
	Pyruvate kinase (PK)	1q21	Rare (2)[a]		May benefit from splenectomy
Redox					
	Glucose 6-phosphate dehydrogenase (G6PD)	Xq28	Common (1)[a]	Very rarely granulocytes	In almost all cases, only AHA from exogenous trigger
	Glutathione synthase	20q11.2	Very rare	CNS	
	γ-Glutamylcysteine synthase	6p12	Very rare	CNS	
	Cytochrome b5 reductase	22q13.31-qter	Rare	CNS	Methemoglobinemia rather than hemolysis
Nucleotide Metabolism					
	Adenylate kinase (AK)	9q34.1	Very rare	CNS	
	Pyrimidine 5′-nucleotidase (P5N)	3q11-q12	Rare (3)[a]		May benefit from splenectomy

[a]The numbers from (1) to (4) indicate the ranking order of these enzymopathies in terms of frequency.

Abbreviations: AHA, acquired hemolytic anemia; CNS, central nervous system; NM, neuromuscular.

TREATMENT PYRUVATE KINASE DEFICIENCY

The management of PK deficiency is mainly supportive. In view of the marked increase in red cell turnover, oral folic acid supplements should be given constantly. Blood transfusion should be used as necessary, and iron chelation may have to be added if the blood transfusion requirement is high enough to cause iron overload. In these patients, who have more severe disease, splenectomy may be beneficial. There is a single case report of curative treatment of PK deficiency by bone marrow transplantation from an HLA-identical PK-normal sibling. This seems a viable option for severe cases when a sibling donor is available. Rescue of inherited PK deficiency through lentiviral-mediated human PK gene transfer has been successful in mice. Prenatal diagnosis has been carried out in a mother who had already had an affected child.

Other glycolytic enzyme abnormalities All of these defects are rare to very rare (Table 129-4), and all cause hemolytic anemia with varying degrees of severity. It is not unusual for the presentation to be in the guise of severe neonatal jaundice, which may require exchange transfusion; if the anemia is less severe, it may present later in life, or it may even remain asymptomatic and be detected incidentally when a blood count is done for unrelated reasons. The spleen is often enlarged. When other systemic manifestations occur, they can involve the central nervous system (sometimes entailing severe mental retardation, particularly in the case of triose phosphate isomerase deficiency), the neuromuscular system, or both. This is not altogether surprising, if we consider that these are housekeeping genes. The *diagnosis* of hemolytic anemia is usually not difficult, thanks to the triad of normomacrocytic anemia, reticulocytosis, and hyperbilirubinemia. Enzymopathies should be considered in the differential diagnosis of any chronic Coombs-negative hemolytic anemia. Unlike with membrane disorders where the red cells show characteristic morphologic abnormalities, in most cases of glycolytic enzymopathies, these are conspicuous by their absence. A definitive diagnosis can be made only by demonstrating the deficiency of an individual enzyme by quantitative assays; these are carried out in only a few specialized laboratories. If a particular molecular abnormality is already known in the family, then one could test directly for that defect at the DNA level, thus bypassing the need for enzyme assays. Of course the time may be getting nearer when a patient will present with her or his exome already sequenced, and we will need to concentrate on which genes to look up within the file. The principles for the management of these conditions are similar as for PK deficiency. In one case of phosphoglycerate kinase deficiency, allogeneic bone marrow transplantation (BMT) effectively controlled the hematologic manifestations but did not reverse neurologic damage.

ABNORMALITIES OF REDOX METABOLISM

Glucose 6-phosphate dehydrogenase (G6PD) deficiency G6PD is a housekeeping enzyme critical in the redox metabolism of all aerobic cells (Fig. 129-1). In red cells, its role is even more critical, because it is the only source of NADPH, which directly and via glutathione (GSH) defends these cells against oxidative stress (Fig. 129-5). G6PD deficiency is a prime example of an HA due to interaction between

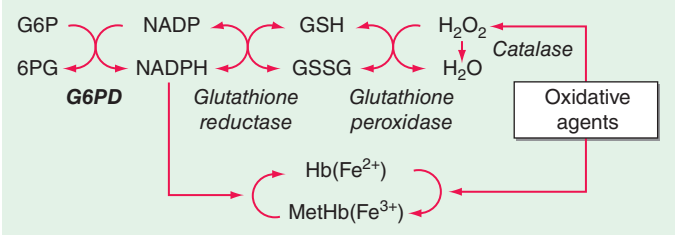

FIGURE 129-5 Diagram of redox metabolism in the red cell. 6PG, 6-phosphogluconate; G6P, glucose 6-phosphate; G6PD, glucose 6-phosphate dehydrogenase; GSH, reduced glutathione; GSSG, oxidized glutathione; Hb, hemoglobin; MetHb, methemoglobin; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate.