REVIEW ARTICLE

G6PD Deficiency

By Ernest Beutler

THIRTY-FIVE YEARS ago Dr William Dameshek, the first editor of the emerging journal *Blood*, invited me to write a review on "The Hemolytic Effect of Primaquine."[1] At the time, primaquine sensitivity, which had just recently been shown to be caused by a deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD),[2] represented a unique example of an inherited deficiency of an enzyme that caused hemolytic anemia.

Although many other red blood cell (RBC) enzyme deficiencies are now known,[3-6] G6PD deficiency still reigns as the most common of all clinically significant enzyme defects, not only in hematology, but in human biology as a whole. A variety of drugs and infections cause hemolytic anemia in persons with the deficiency, and nonhematologic sequelae have been claimed as well. Using classical biochemical techniques, enormous apparent diversity of mutations causing G6PD deficiency was documented in hundreds of publications. The distribution of the deficiency in different populations has been investigated exhaustively, and gene frequencies of over 0.5 have been observed in some ethnic groups. With the advances made possible by the cloning of G6PD cDNA and gene[7,8] has come a better understanding of the diversity that exists. In this review, I will attempt to put what we have learned in the past 35 years into perspective and to touch upon what still needs to be learned.

CLINICAL MANIFESTATIONS

Hemolytic Anemia

Drug-induced hemolysis. G6PD deficiency was discovered as a result of a series of investigations performed to understand why some persons were uniquely sensitive to the development of hemolytic anemia when they ingested the 8-aminoquinoline antimalarial drug primaquine.[9] Thus, the first and best-known morbid effect of G6PD deficiency was drug-induced hemolysis. Primaquine is but one of many drugs that shortens RBC life span in G6PD-deficient persons (see below). The administration of such drugs is followed, after a 1- or 2-day delay, by a fall in the hemoglobin (Hb) concentration. Heinz bodies, particles of denatured protein adherent to the RBC membrane, appear in the early stages of drug administration and disappear as hemolysis progresses.[10] Another morphologic feature observed on the blood film is the appearance of RBCs that have variously been designated "irregularly contracted RBCs," "eccentrocytes," "hemighosts," "double-colored RBC," and "cross-bonded cells." The Hb of these cells is confined to one side of the erythrocyte, leaving the other part as a flat, Hb-free ghost. In this portion of the cell, the inside surface of the membrane is tightly bonded.[11] Often Heinz bodies are included in the flattened region, where they may bulge visibly out of the leaflet.[12] When hemolysis is severe, the urine turns dark and the patient may complain of back pain. When G6PD deficiency is relatively mild, as in the class 3 G6PD A−,* the hemolytic anemia is self-limited[10] because only the older RBCs are destroyed[14] and young RBCs have normal or near-normal enzyme activity. In patients with more severe forms of enzyme deficiency such as G6PD Mediterranean, young cells are severely deficient in G6PD,[15] and as a consequence, hemolysis continues until well after the administration of drug is stopped.[16,17]

The fact that primaquine was only one of many drugs that precipitated hemolysis in G6PD-deficient individuals was recognized early in our studies by in vivo challenge of ^{51}Cr-labeled erythrocyte.[18] Therefore, in the 1950s, when a person with G6PD deficiency developed hemolytic anemia, it was generally assumed that hemolysis had been precipitated by a drug, and whatever drug had been ingested was considered to be culpable. As a result, a long list of drugs thought to cause hemolysis evolved. On more careful study many of them have been proven to be quite innocent with respect to the cause of hemolytic anemia in G6PD deficiency.[19]

As a matter of fact, it is difficult to be certain in some cases, whether a cause-and-effect relationship exists between ingestion of a drug and hemolysis. The most robust data regarding the potential hemolytic effect of drugs and chemicals comes from clinical investigations with ^{51}Cr-labeled erythrocytes. However, even results obtained using RBC survival studies can be misleading. Individual inherited differences in drug metabolism such as acetylator status play a significant role in determining whether a drug will be hemolytic.[18,20,21] Thus, if a recipient who efficiently catabolizes the active hemolytic metabolite of a drug is challenged, hemolysis will not be apparent, but the drug may be hemolytic in a subset of individuals who metabolize the drug less efficiently. Moreover, even when a drug does shorten RBC life span, as shown by performing sensitive studies with ^{51}Cr-labeled erythrocytes, the degree of hemolysis may be so modest as to be of no clinical significance.[22] Sulfamethoxazole, a component of the commonly used combination Septra® and Bactrim®, has been shown to produce shortening of the

* G6PD variants have been classified[13] as follows: class 1, hereditary nonspherocytic hemolytic anemia; class 2, severe deficiency; class 3, mild deficiency; class 4, not deficient variant.

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Table 1. Drugs and Chemicals That Should Be Avoided by Persons With G6PD Deficiency

Acetanilid	Primaquine
Furazolidone (Furoxone)[356,357]	Sulfacetamide
Methylene Blue	Sulfamethoxazole (Gantanol)
Nalidixic acid (NegGram)	Sulfanilamide
Naphthalene	Sulfapyridine
Niridazole (Ambilhar)	Thiazolesulfone
Isobutyl nitrite[358]	Toluidine blue
Naphthalene[359,360]	Trinitrotoluene (TNT)
Nitrofurantoin (Furadantin)	Urate oxidase[362]
Phenazopyridine (Pyridium)[361]	Phenylhydrazine

Unless otherwise indicated, references given in reference 19.

RBC life span[23] in Asian subjects with G6PD deficiency, but no significant hemolysis could be shown when this combination was used clinically in patients with G6PD A−.[24] RBCs from subjects with severe class 2 variants such as G6PD Mediterranean may be sensitive to drugs when those with milder defects such as G6PD A− are not. The data obtained from ^{51}Cr survival must be supplemented with less reliable information gained from clinical observations. Clinical studies are confounded by the effect of intercurrent infections which may be responsible for hemolysis rather than the drug that has been administered. For example, the clinical observations that hemolytic anemia is caused by acetaminophen have been made during the concurrent presence of infection[25]; investigations of the putative hemolytic effect of this drug with ^{51}Cr-labeled erythrocytes fail to show shortening of RBC life span.[26,27] Reports of single cases implicating agents such as melphalan,[28] dimercaprol,[29] doxorubicin,[30] and sodium metasophan noramidipyrine[31] are difficult to interpret. When more than a decade has passed without any confirming report, one is inclined to regard the originally reported episode as being coincidental rather than etiologic.

Detailed analysis of the evidence regarding the hemolytic potential of a large number of drugs and chemicals has been published previously.[19] Table 1 lists drugs and chemicals that appear, on the basis of the available evidence, to cause clinically significant hemolytic anemia. Drugs that can be given safely to G6PD-deficient persons are listed in Table 2.

Favism. A clinical manifestation of G6PD deficiency closely related to drug-induced hemolysis is the hemolytic anemia induced by ingestion of the fava bean, *Vicia faba*. Favism, this hemolytic anemia, has been known since antiquity. Indeed, the demise of Pythagoras has been attributed to unwillingness to enter a bean field, possibly because of favism,[32] although the evidence supporting this interpretation is feeble. Patients with favism are always G6PD deficient, but not all G6PD-deficient individuals develop hemolysis when they ingest fava beans. Thus, G6PD deficiency is a necessary but not sufficient cause of favism. Presumably some other factor, probably also genetic[33] and very likely related to metabolism of the active ingredients in the beans, is involved. The vast majority of cases of favism occurs in individuals with severely deficient (class 2) variants of G6PD, but occasionally favism has been observed in a patient with G6PD A−.[34,35] Although at times the onset of hemolysis in favism may be more explosive than occurs as a result of drug administration,[36] in general the course of hemolysis in favism is very similar to that occurring after drug ingestion. Hemolysis does not usually begin for 24 hours after ingestion of the beans and hemoglobinuria may continue for several days.[11]

Mechanism of hemolysis. The mechanism by which drugs and fava beans produce hemolytic anemia is not well understood. Such drugs do not lyse RBCs in vitro.[37] Instead, they appear to inflict oxidative injury on the erythrocytes and, therefore, are often designated as oxidative drugs. Because of its relatively high frequency in some areas in the Mediterranean region, the mechanism by which fava beans produce hemolysis has received special attention, with the suggestion that the pathogenesis of favism and drug-induced hemolytic anemia may be essentially the same.[11] Vicine, convice, ascorbate, and L-DOPA are abundant in fava beans and have been considered candidate toxins. The most likely offenders are vicine and convicine, β-glucosides of pyrimi-

Table 2. Some Common Drugs That Can Safely Be Administered in Therapeutic Doses to G6PD-Deficient Subjects Without Nonspherocytic Hemolytic Anemia

Acetaminophen (paracetamol, Tylenol, Tralgon, hydroxyacetanilid)
Acetophenetidin (phenacetin)
Acetylsalicylic acid (aspirin)
Aminopyrine (Pyramidon, amidopyrine)
Actazoline (Antistine)
Antipyrine
Ascorbic acid (vitamin C)*
Benzhexol (Artane)
Chloramphenicol
Chlorguanidine (Proguanil, Paludrine)
Chloroquine
Colchicine
Diphenylhydramine (Benadryl)
Isoniazid
L-Dopa
Menadione sodium bisulfite (Hykinone)
Menapthone
p-Aminobenzoic acid
Phenylbutazone
Phenytoin
Probenecid (Benemid)
Procainamide hydrochloride (Pronestyl)
Pyrimethamine (Daraprim)
Quinidine
Quinine
Streptomycin
Sulfacytine
Sulfadiazine
Sulfaguanidine
Sulfamerazine
Sulfamethoxypyridazine (Kynex)
Sulfisoxazole (Gantrisin)
Tiaprofenic acid[18]
Trimethoprim
Tripelennamine (Pyribenzamine)
Vitamin K

Unless otherwise indicated, references given in reference 19.

* Very high "therapeutic" doses (~80 g administered intravenously) have precipitated severe, even fatal, hemolysis.[363-365]

dine compounds that are converted by β-glucosidases to their aglycones, vicine and isouramil, respectively. These compounds form reactive semiquinoid-free radicals and can generate active oxygen species. This results in the formation of ferrylhemoglobin, methemoglobin, and inactivation of various enzymes. The reactions that occur are complex and varied and, therefore, largely unpredictable.[11,38-44]

New drugs continue to be introduced into medical practice, and it would be extremely useful to be able to predict which of these cannot safely be given to patients with G6PD deficiency. Unfortunately those drugs that do produce hemolysis have no clearly understood common denominator either in structure or in chemical properties. Moreover, in some (perhaps in most) instances the injury to the enzyme-deficient erythrocyte is not mediated by the chemical compound that is administered, but rather by a metabolic product. In vitro systems have been devised in an attempt to mimic what occurs in the body.[45-48] The RBCs of some animal species, notably sheep,[49] regularly have low RBC G6PD levels. Moreover, hereditary deficiencies occurring within species are documented,[50-54] but these have limited appeal with respect to attempts to predict the hemolytic potential of drugs because of species differences in drug metabolism and of RBC metabolism.

Infection-induced hemolysis. Although, for historical reasons, drug-induced hemolysis has attracted the most attention, it is likely that hemolysis induced by infection may be a more common cause of clinically significant hemolysis. Numerous reports attest to the importance of infection in causing hemolytic anemia.[25,55-88] It is clear that many different types of infections may trigger hemolysis in the G6PD-deficient patient. The mechanism by which this occurs is not clear, but an imaginative suggestion has been that during phagocytosis, leukocytes damage erythrocytes in their environment by discharging active oxygen species during phagocytosis.[72] Perhaps nitric oxide might also play such a role.[89] It is unlikely that such a mechanism is operative in the case of viral infections such as hepatitis, but it may play a role in some infections.

Diabetes mellitus-induced hemolysis. It has been suggested that episodes of diabetic acidosis[61,90] may precipitate hemolytic episodes in persons with G6PD deficiency, but in one study, no evidence was found that such an effect existed.[91] It has also been reported that hypoglycemia may precipitate hemolysis in G6PD deficiency.[92]

Hereditary nonspherocytic hemolytic anemia. It was in 1958,[93] not long after G6PD deficiency was identified as the cause of primaquine sensitivity, that it was recognized that the enzyme deficiency could cause chronic hemolysis as well. The syndrome of hereditary nonspherocytic hemolytic anemia did not occur in persons who inherited the common, polymorphic variants of G6PD such as G6PD A− or G6PD Mediterranean, but rather in patients who had inherited rare mutations, designated class 1 because of their association with chronic hemolysis. (Exceptional instances in which class 2 variants have seemed to be associated with chronic hemolytic anemia[94,95] are discussed below). The severity of hemolysis varies greatly. Although it is usually mild, the patient with "G6PD Campinas^{1463T}"[96] has transfusion-dependent hemolysis resembling thalassemia major.

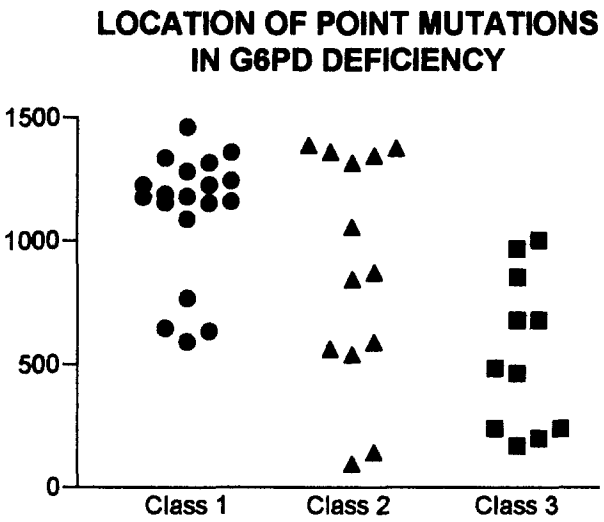

Fig 1. The distribution along the G6PD sequence of point mutations causing G6PD deficiencyis shown. Class 1 (●, nonspherocytic hemolytic anemia), class 2 (▲, severe deficiency), and class 3 (■, moderate to mild deficiency) tend to have different distributions. Class 1 mutants, in particular, tend to be clustered in the region of the putative glucose-6-phosphate binding site (amino acid 205; cDNA nucleotides 613-615) and putative NADP-binding site (amino acids 386 and 387; nucleotides 1,156-1,161).

Presumably class 1 variants produce chronic hemolysis because the functional severity of the defect is so great that the erythrocyte cannot even withstand the normal stresses that it encounters in the circulation. The functional severity in these patients is not usually reflected by the level of the enzyme as it is measured in the laboratory. The RBCs of patients with class 1 variants may have residual G6PD activity as high as 35% of normal[97] when measured under standard conditions. The functional impairment that leads to the shortening of the RBC life span in these patients may include such factors as susceptibility to inhibition by NADPH[98] and in vivo lability.[99] Possibly the most consistent common feature of class 1 variants is the location of the mutation. In the great majority of cases, it is in the region of the putative NADP-binding or glucose-6-phosphate binding site of the molecule. (see below and Fig 1)

Neonatal Jaundice

Neonatal jaundice is one of the most life- and health-threatening consequences of G6PD deficiency, and kernicterus may occur in these infants.[100-103] It is often erroneously assumed that the jaundice is the result of hemolysis. However, this is apparently not usually the case. Anemia is not present in G6PD-deficient infants that develop neonatal icterus.[104] Instead of the icterus being a manifestation of accelerated RBC destruction, it now seems likely that it is largely the result of the impairment of liver function, presumably because of a deficiency of the enzyme in the liver. It is entirely possible that some shortening of RBC life span also plays a role.[105] Neonatal jaundice has occurred primarily in Asian[106-108] and Mediterranean[104,109-111] infants. In one study,[103] G6PD Aures^{143C} has been associated with a particu-

larly high incidence of jaundice. Early reports from the United States suggested that African-American infants did not have a significantly increased incidence of neonatal jaundice.[112-114] However, anecdotal observations from the United States[115] and surveys in Jamaica[100] and in Africa[116-118] all suggest that an increased incidence of neonatal icterus may occur also in infants with G6PD A−.

Transfusion With G6PD-Deficient Blood

There is evidence that G6PD-deficient RBCs maintain viability less well than do normal cells even without being subjected to oxidative stress.[119] However, the consequences of transfusing a single unit of G6PD-deficient RBCs into an adult are probably minor. It has been pointed out that in the case of G6PD A−, the number of cells that would be destroyed if a hemolytic stress occurred would be no greater than the number of nonviable cells in a unit of blood nearing its expiration date.[120] Transfusion of G6PD-deficient blood may be an issue of greater potential importance in parts of the world in which the incidence of the defect is very high and where more severely deficient class 2 variants such as G6PD Mediterranean are prevalent. In such areas, it is possible for a patient to receive, by chance, several units of deficient blood. In one instance, it has been suggested that fatal hemolysis occurred in a young woman as a result of receiving G6PD-deficient blood,[121] but the reports of such severe consequences are not themselves convincing of a cause-and-effect relationship. In a controlled study, only minor increases in bilirubin levels were found in individuals receiving a unit of severely G6PD-deficient blood,[122] but the changes might be greater if a hemolytic stress were present.

In general, it has not been the practice to screen blood bank blood for G6PD deficiency, even in areas in which the gene frequency is very high.[123] However, caution is justified in the exchange transfusion of newborn infants. Here, in contrast to adults, the proportion of deficient cells could be very high, and the products of Hb catabolism disposed of inefficiently by the immature liver.[124-126]

Other Manifestations of G6PD Deficiency

It is reasonable to assume that a genetic trait that has reached such high frequencies in many populations that it is carried by some 200,000,000 persons would not have a readily apparent effect on fitness. For this reason, if no other, it has been generally assumed that those who carry polymorphic genes for G6PD deficiency would not suffer from any morbidity. Nonetheless, a number of studies have suggested that G6PD-deficient individuals might, even in the absence of any stress, have some clinical abnormalities.

Tissue distribution of the deficiency. Early studies indicated that the deficiency of G6PD activity was limited to the RBCs; liver and leukocyte activity was reported to be normal, and it was even suggested that the defect might not be in the G6PD gene itself, but rather some other gene that influenced the stability of the enzyme in the erythrocyte.[127] Platelet activity was found to average about 40% of normal.[128]

These studies were probably performed on patients with G6PD A−, and subsequent investigations in patients with more severely deficient variants indicated that other tissues were indeed involved in G6PD deficiency. Mediterranean subjects were found to have leukocyte enzyme activity that was only 22%[129] and 39%[130] of normal, platelet activity that was 19% of normal,[129] saliva activity that was 7% of normal,[131] and liver activity that was 60% of normal.[132] In one study of liver biopsy samples, marked variability in the level of enzyme was found, but the activity was consistently lower in G6PD A− subjects than in most subjects who did not have RBC G6PD deficiency.[133] G6PD activity could not be detected in the breast milk of severely deficient mothers.[134] Cultured fibroblasts from a deficient male from Ferrara, Italy had only 10% of normal G6PD activity.[135] In Chinese patients with severe RBC enzyme deficiency, the leukocyte G6PD activity was 25% of normal, platelets 28% of normal, liver 49% of normal, adrenal 13% of normal and kidneys 13% of normal.[136] Lenses from patients with G6PD A− were found to contain about 40% of normal activity[137] and cataractous lenses of Mediterranean subjects were devoid of detectable enzyme when cataracts of patients with normal erythrocyte G6PD levels averaged 5 mU/mg protein.[138]

Hematologic effects. In our original studies of G6PD deficiency, ^{51}Cr erythrocyte survival was determined on many primaquine sensitive subjects, who now would be designated as being hemizygotes for G6PD A−. The baseline RBC survivals of these subjects was normal.[10,18,139] Subsequently, studies of ^{32}DFP and ^{51}Cr RBC survival in such G6PD A− subjects were claimed to show marked shortening of the erythrocyte life span, with a mean ^{51}Cr half-life of only 20.2 in three subjects with a control mean of 28.7.[140] The average ^{32}DFP-labeled RBC half-life of G6PD-deficient subjects was reported to be 48 days with a mean normal of 66.1 days.[140] Such shortening of RBC life-span has not been observed either before or after this one investigation, even with much more severe forms of G6PD deficiency, and the finding of marked shortening of RBC life span in G6PD A− subjects in the absence of a stress cannot be regarded as valid. However, some minimal shortening of RBC life span has been observed in some studies of Mediterranean subjects with G6PD deficiency: mean ^{51}Cr half-lives of 22.9 days,[141] 26 days,[142] and 28.9 days.[143] Interestingly, even though the RBC life span of these subjects is nearly normal, three reports document a slight decrease in the Hb concentration of the blood of normal subjects with the Mediterranean form of G6PD deficiency.[144-146] In one of these studies,[145] the mean difference between the Hb levels of deficient and normal subjects was nearly 2 g/dL and was accompanied by an increase in the average reticulocyte count of 0.28%, and of the mean corpuscular volume of 3.9 fL, all of these differences being statistically significant. There have also been occasional cases of apparent G6PD Mediterranean with low-grade hemolysis,[94,95] although these studies were performed before verification of the genotype by DNA analysis was possible. Thus, it appears that under certain circumstances, either genetic or environmental, low-grade hemolysis can occur in persons with G6PD Mediterranean. It is doubtful whether this actually occurs in the milder, class 3 variants such as G6PD A−.

Life expectancy. Large-scale studies have assessed the effect of G6PD A− on the overall health of Afro-American

Table 3. Putative Abnormalities Suggested to Occur in Persons With G6PD Deficiency

Proposed Effect	Evidence	Class*	Reference	Contradictory Reference
Platelet abnormalities	A	2	366, 367	368
Skin pedicle flap loss	A	3	369	
Athletic performance, impairment	C	3	370	
Seizure disorders	A	1, 2	371, 372	
Cataracts, increased incidence	A	1	371, 373-375	377
	C	2	376	378, 379
Manifestations of schizophrenia or depression	C	3	192, 380	381
Renin release, impairment	C	2	382	
Glucose tolerance tests, abnormalities or diabetes	C	3	383, 384	385-387
Insulin release, abnormalities	C		386	
Cortisol production, decrease	C	2, 3	388	389
Survival, decrease	C	3	147	
Cardiovascular disease, risk factor	C	3	390	391
Cholelithiasis	C	2	392	
Myoglobuinuria	A	2	393, 394	
Susceptibility to infection, increased	C	21	395	
	A		396	397
Coronary artery disease, decreased incidence	C	3, 4	398	
Leukocyte function, abnormality	A	12	396, 399	400
Increased jaundice in hepatitis	A	2	401	
Mental retardation	C	2	402	
Dehydroepiandrostrone sulfate, increased serum levels	C	2	403	

Abbreviations: A, anectodal; C, controlled series.

* Class 1, hereditary nonspherocytic hemolytic anemia; class 2, severe deficiency; class 3, mild deficiency; class 4, not deficient (eg, G6PD A+[13]). Classification based on racial origin if data not given.

veterans. In an investigation of 1,413 black males Petrakis et al[147] found that the incidence of G6PD deficiency was 12.1% in the 5- to 20-year age group, 5.6% in the 21- to 49-year age group, and only 3.8% of those above the age of 49. While acknowledging that there might be a number of explanations for this, they concluded that G6PD-deficient subjects had a reduced life span. However, this seems unlikely in view of the fact that it would require a very high excess mortality rate among persons with G6PD deficiency. Indeed, a study of 65,154 black male patients admitted to US Veteran's Administration hospitals showed no increased mortality among patients who were G6PD deficient and no significant difference in the mean ages of G6PD-deficient and -nondeficient patients.[148]

Cancer. Epidemiologic studies suggested to some that the incidence of cancer may be lower in G6PD-deficient persons.[149-153] However, these investigations were generally based on screening methods that do not efficiently ascertain G6PD deficiency in heterozygotes, and even in hemizygotes who have a disorder that might decrease RBC life span. Indeed, in one study[154] it was shown that the RBC G6PD activity of cancer patients is higher than that of controls. More recent studies tend not to show any differences between the incidence of cancer in G6PD-deficient and normal subjects.[154,155]

Other putative clinical and laboratory abnormalities. The many other possible clinical and laboratory consequences of G6PD deficiency that have been proposed, either on the basis of anecdotal observations or more detailed studies are summarized in Table 3. In many instances, contradictory data have also been presented and it is difficult to judge the validity of the many claims that have been made.

THE ENZYME

Structure

The G6PD monomer consists of 515 amino acid subunits with a calculated molecular weight of 59,256 daltons. The active enzyme exists as a dimer[156,157] and contains tightly bound NADP.[158,159] Aggregation of the inactive monomers into catalytically active dimers and higher forms requires the presence of NADP.[160] Thus, NADP appears to be bound to the enzyme both as a structural component and as one of the substrates of the reaction.[158,161,162] The binding sites for this coenzyme have not been identified at the structural level, but examination of mutants has suggested that amino acids 386 and 387, the basic amino acids lysine and arginine, respectively, seem to bind one of the phosphates of NADP.[163] The evidence that this site is involved in the binding of NADP is as follows: (1) all mutants that rapidly lose activity at a 10 μmol/L NADP concentration, but are reactivated at high concentrations of NADP have been shown to have mutations in this region; (2) mutations in this region result in paradoxical electrophoretic migration of the enzyme as if it had become more positively charged, even when the amino acid change adds a negative charge, suggesting failure of binding of negatively charged NADP. It has also been suggested, on the basis of the deduced conformation of the peptide chain of the yeast enzyme, that the NADP binding site may be elsewhere,[164] but the data on the human enzyme seems much more compelling to me. The glucose-6-phosphate binding site has been identified at amino acid 205 by locating a lysine at this position that is reactive with pyridoxal phosphate in competition with glucose-6-phosphate.[165-168]

Table 4. G6PD Variants That Have Been Characterized at the DNA Level

Variant	Nucleotide Substitution	WHO Class	Amino Acid Substitution	References
Gaohe	95 A → G	2	32 His → Arg	404
Gaozhou				
"Sunderland"	105-107 del	1	35 Ile → del	405
"Aures"	143 T → C	2	48 Ile → Thr	406
Metaponto	172 G → A	3	58 Asp → Asn	407
A-				204
Distrito Federal				408
"Matera"				407
Castilla	202 G → A 376 A → G	3	68 Val → Met 126 Asn → Asp	408
Alabama				409
Betica				242
Tepic				408
Ferrara				410
Ube	241 C → T	3	81 Arg → Cys	411
Konan				
"Lagosanto"	242 G → A	3	81 Arg → His	412
"Vancouver"	317 C → G 544 C → T 592 C → T	1	106 Ser → Cys 182 Arg → Trp 198 Arg → Cys	413
São Borga	337 G → A	4	113 Asp → Asn	414
A	376 A → G	4	126 Asn → Asp	415
"Chinese-4"	392 G → T	?	131 Gly → Val	416
"Ilesha"	466 G → A	3	156 Glu → Lys	407
Mahidol	487 G → A	3	163 Gly → Ser	417
Plymouth	488 G → A	1	163 Gly → Asp	418
"Chinese-3"	493 A → G	2	165 Asn → Asp	218
"Shinshu"	527 A → G	1	176 Asp → Gly	419
Santamaria	542 A → T 376 A → G	2	181 Asp → Val 126 Asn → Asp	420
Mediterranean				407
Dallas				268
Birmingham	563 C → T	2	188 Ser → Phe	268
"Sassari"				421
"Cagliari"				421
Panama				409
"Coimbra"	592 C → T	2	198 Arg → Cys	422
"Santiago"	593 G → C	1	198 Arg → Pro	423
Sibari	634 A → G	3	212 Met → Val	251
Minnesota				
Marion	637 G → T	1	213 Val → Leu	216
Gastonia				
"Harilaou	648 T → G	1	216 Phe → Leu	217, 420
"Mexico City"	680 G → A	3	227 Arg → Gln	423

(Continued on following page)

Table 4. G6PD Variants That Have Been Characterized at the DNA Level (Cont'd)

Variant	Nucleotide Substitution	WHO Class	Amino Acid Substitution	References
A-	680 G → T 376 A → G	3	227 Arg → Leu 126 Asn → Asp	204
"Stonybrook"	724-729 GGC del	1	242-243 Gly & Thr	219
Wayne	769 G → C	1	257 Arg → Gly	424
"Cleveland"	820 G → A	1	274 Glu → Lys	219
"Chinese-1"	835 A → T	2	279 Thr → Ser	250
Seattle				421
Lodi	844 G → C	2	282 Asp → His	393
"Modena"				425
"Montalbano"	854 G → A	3	285 Arg → His	426
Viangchan	871 G → A	2	291 Val → Met	424
Jammu				
"West Virginia"	910 G → T	1	303 Val → Phe	219
Kalyam	949 G → A	3	317 Glu → Lys	427
Kerala				
A-	968 T → C 376 A → G	3	323 Leu → Pro 126 Asn → Asp	204
Betica				
Selma				
"Nara"	953-976 del	1	319-326 del	428
Chatham	1003 G → A	3	335 Ala → Thr	407
"Fushan"	1004 C → A	2	335 Ala → Asp	219
"Chinese-5"	1024 C → T	?	342 Leu → Phe	416
"Ierepetra"	1057 C → T	2	353 Pro → Ser	423
Loma Linda	1089 C → A	1	363 Asn → Lys	216
"Olomouc"	1141 T → C	1	381 Phe → Leu	219
Tomah	1153 T → C	1	385 Cys → Arg	407
Iowa				
Walter Reed	1156 A → G	1	386 Lys → Glu	163
Iowa City				
Springfield				
Guadalajara	1159 C → T	1	387 Arg → Gys	423
"Mt. Sinai"	1159 C → T 376 A → G	1	387 Arg → Cys 126 Asn → Asp	248
Beverly Hills				163
Genova	1160 G → A	1	387 Arg → His	429
Worcester				409
"Praba"	1166 A → G	1	389 Glu → Gly	219
Nashville				
Anaheim	1178 G → A	1	393 Arg → His	216
"Calgary"				430
"Portici"				
Alhambra	1180 G → C	1	394 Val → Leu	423
"Puerto Limon"	1192 G → A	1	398 Glu → Lys	420

(Continued on following page)

Table 4. G6PD Variants That Have Been Characterized at the DNA Level (Cont'd)

Variant	Nucleotide Substitution	WHO Class	Amino Acid Substitution	References
Riverside	1228 G → T	1	410 Gly → Cys	163
"Japan"	1229 G → A	1	410 Gly → Asp	423
"Shinagawa"				419
Tokyo	1246 G → A	1	416 Glu → Lys	431
"Georgia"	1284 C → A	1	428 Tyr → End	219
"Varnsdorf"	3' intron 10 splice site del	1	N/A	219
Pawnee	1316 G → C	2	439 Arg → Pro	423
Telti	1318 C → T	1	440 Leu → Phe	418
Kobe				432
"Santiago de Cuba"	1339 G → A	1	447 Gly → Arg	407
"Cassano"	1347 G → C	2	449 Gln → His	251
Union	1360 C → T	2	454 Arg → Cys	249, 250
Maewo				247, 251
Andalus	1361 G → A	1	454 Arg → His	433
Cosenza	1376 G → C	2	459 Arg → Pro	251
Taiwan-Hakka				
Gifu-like	1376 G → T	2	459 Arg → Leu	434
				435
Kaiping				
Anant	1388 G → A	2	463 Arg → His	434
Dhon				
Petrich				
Sapporo				
"Campinas"	1463 G → T	1	488 Gly → Val	96

Class 1, nonspherocytic hemolytic anemia; class 2, severe deficiency; class 3, moderate deficiency; class 4, not deficient.

Enzymology

G6PD catalyzes the first step in the hexose monophosphate pathway (HMP). It oxidizes glucose-6-phosphate to 6-phosphogluconolactone, reducing NADP to NADPH. The HMP is the only source of NADPH in the erythrocytes and it also serves to produce the ribose needed for synthesis of nucleotides in the salvage pathways. The main function of the pathway seems to be to protect the RBC against oxidative damage. Glutathione peroxidase (GSHPx) removes peroxide from the erythrocyte.[169] Reduced glutathione (GSH) serves as a substrate for this enzyme, and because NADPH is required for the reduction of oxidized glutathione and protein sulfhydryl groups,[170] it is an essential factor in the chain of reactions that defends the RBC against peroxide. RBCs are a particularly rich source of catalase, but this enzyme is relatively inefficient at removing low levels of peroxide levels. Moreover, catalase has the ability to bind NADPH tightly[171,172] and the inactive form, compound II, is reactivated by NADPH. Thus, the activity of the HMP serves to remove peroxide not only through the action of GSHPx, but also by activating catalase.[172] The long-standing controversy about which is the more important, catalase or GSHPx,[169,173-176] seems to me to be largely irrelevant and futile. Clearly, both enzymes may play a role and serve as backup mechanisms for each other. Which is more active at any one time may depend on the particular conditions under which the measurements are being made and very likely the particular peroxide substrate that is being catabolized.

The K_m of G6PD for NADP is very low, roughly 2 to 4 μmol/L, and the enzyme is strongly inhibited competitively by NADPH. Thus, the NADPH/NADP ratio within the RBC controls the rate of the reaction in an autoregulatory manner. In the quiescent state, the NADPH/NADP ratio is very high,[177,178] and G6PD is nearly completely inhibited. When NADPH is oxidized, as when oxidized glutathione is reduced in the glutathione reductase reaction, NADPH is converted to NADP and G6PD becomes active, reducing NADP to NADPH. G6PD-deficient cells are unable to respond adequately to such an oxidative stress. When the susceptibility of a mutant enzyme to inhibition by NADPH is greater than normal, this compounds the metabolic difficulty of the cell.[98]

GENETICS

X-Linkage and X-Inactivation

Even before the basic defect was known, X-linkage of primaquine sensitivity was established by application of the glutathione stability test,[179] the earliest reliable means for

the detection of the defect of primaquine sensitivity. Pedigrees of Afro-American families showed[180] that glutathione instability was most frequently transmitted from mother to son, although there were instances in which the defect could not be detected in the mother and even where apparent father-to-son transmission occurred. It was correctly presumed that these anomalies were caused by inadequate ascertainment of heterozygous females with the relatively crude technology then available. With the recognition that the basic defect was a deficiency of G6PD, X-linkage was confirmed by estimation of enzyme activity,[181] studies of electrophoretic mobility,[182] and study of linkage with color blindness.[183] Still, there were families in which genetic transmission aberrant for X-linkage was observed.[184] These aberrations led us to suggest that one of the two X-chromosomes might be inactive in human females,[185,186] at the same time and quite independently of the proposal made by Lyon on the basis of X-linked traits in mice.[187]

More recently, it has been appreciated that G6PD is one of a cluster of genes on the distal long arm of the X chromosome (q28). Included in this group of genes are those for the fragile X,[188] hemophilia A,[189] color vision,[190,191] a putative gene for bipolar affective illness,[192] the ABP-280 filamin gene (FLN[1]),[193] Bornholm eye disease,[194] clasped-thumb mental retardation (MASA) syndrome,[195] and dyskeratosis congenita.[196]

The G6PD Gene

G6PD was cloned and sequenced by Persico et al[7,197-199] and then independently by Takizawa and Yoshida.[8] The gene contains 13 exons and is over 20 Kb in length. The first exon contains no coding sequence and the intron between exons 2 and 3 is extraordinarily long, extending for 9,857 bp. The sequence of the entire gene is known.[200] At the 5′ end of the gene is a cytidine-guanine dinucleotide (CpG)-rich island. Differential demethylation of some of the CpG's is associated with expression of the gene on the active X chromosome[201] and this island appears to be preserved between man and mouse.[202] A 2,850-bp segment of the 5′ end has been fused to a reporter and deletional analysis showed that a 436-bp domain was sufficient for full expression.[203]

Some heterogeneity of G6PD mRNA has been found, but its functional significance is doubtful. The existence of an alternatively spliced form has been documented,[204-206] but the amount of this mRNA, which contains 138 nucleotides of what is usually the 3′ end of intron 7 without losing frame, is always very small. Production of the enzyme has been accomplished in vitro in Cos cells[207] and in *Escerichia coli*.[208-210] A suggestion[211] that G6PD was, in reality, a translation product made from two separate mRNAs has proved to be based on an artifact.[212-215]

Mutations

Biochemical characterization has led to the description of no less than 442 variants of G6PD believed to be distinct. Two hundred ninety nine of these were characterized by methods agreed upon by a World Health Organization (WHO) expert group[13] and were considered, at least by those who described them, as being different from the others that had been published. Because most mutants of G6PD had abnormal properties (either electrophoretic, kinetic, or both), it was to be expected that the mutations affecting this enzyme would be found in the coding region. This has indeed proven to be the case. Facile polymerase chain reaction (PCR)-based methods for the detection of mutations have been developed,[216-218] and these have made it possible to define the mutations in many individuals (Table 4).

Distribution and nature of mutations. As of this writing, 60 mutations or combination of mutations have been documented in G6PD (Table 4); all but one of these are associated with enzyme deficiency. The types of mutations found are more restricted than is the case with many other genes. It appears that total G6PD deficiency is not compatible with life. Thus, most mutations are missense point mutations and deletions (of which three are known) and are found in multiples of three nucleotides so that a frameshift does not occur. Only one splicing mutation has been found and no promoter mutations have been identified. There is only one exception to the rule that mutations found in patients do not preclude the synthesis of enzyme; a mutation that we have designated "Georgia" changes Tyr^{428} to a stop codon.[219] Eighty-three percent of the peptide chain would have been synthesized by the time the stop codon were encountered. Perhaps the truncated protein made is partially functional. It is also noteworthy that the mutation was found in a female heterozygote, and it is conceivable that unbalanced X-inactivation helped to prevent the dire consequences that might otherwise have been expected from a null mutation.

The distribution of mutations along the length of the cDNA is also not random, as shown in Fig 1. Point mutations that cause the formation of class 1 variants, which are those associated with nonspherocytic hemolytic anemia, are largely confined to two areas, one of which approximates the NADP or NADPH binding site of the enzyme and the other of which is in the region of the glucose-6-P binding site. As shown in Table 4, of the 23 point mutations that are associated with class 1 variants, 5 cause substitutions in the amino acid range 198 to 257 and 15 in the range of 363 to 447. Thus, 87% of these mutations are found in two areas that comprise only 28% of the polypeptide. There are, of course, exceptions and cases in which changing a single codon produces different clinical syndromes. Thus, changing Met^{212} to Val produces a class 1 variant, G6PD Santiago, whereas changing the same amino acid to Cys produces the class 2 variant Coimbra. Similarly, the common class 2 variant G6PD Union is the result of a mutation of Arg^{454} to Cys, whereas a change of the same amino acid to His produces a variant, G6PD Andalus, associated with mild hemolytic anemia.

Frequency of mutations in various populations. The frequency of G6PD deficiency differs markedly among different populations. Among black Americans, the gene frequency of enzyme deficiency is 0.10 to 0.11.[148,220] The frequency of G6PD Mediterranean^{563T} is 0.70 among Kurdish Jews,[221] probably the highest incidence of G6PD deficiency in any population. In a Greek survey of over 1,200,000 infants, a gene frequency of 0.045 was documented.[222] In Asia too, high frequencies are encountered.[223-225] Detailed population frequency data may be found in a number of comprehen-

sive reviews,[19,226,227] but these data were compiled before mutation analysis was possible.

In the era before mutation identification was possible at the DNA level, it was generally recognized that certain types of mutations were characteristic of certain populations. The electrophoretic mobility of deficient samples from Africans was almost always rapid, and the variant characteristic of this ethnic group was designated G6PD A−,[182] in contradistinction to the electrophoretically rapid, normally active G6PD A+ enzyme found in the same population. The more severe deficiency, found in Mediterranean populations, in which the residual enzyme had a normal electrophoretic mobility was designated G6PD Mediterranean.[228] However, on the basis of biochemical characterization it was believed that there was great heterogeneity among the different variants found in this region of the world.[229-232] In Asia too, many different variants were characterized.[233-241]

With development of the ability to define the mutations in the G6PD gene, some aspects of the situation became more complicated, but others were simplified. G6PD A−, which had generally been regarded as a distinct, homogeneous mutation, proved to be the result of the superimposition of several point substitutions on the background of G6PD A+^{376G}. The mutation always found in G6PD A−^{376G} is characteristic of G6PD A+. In most cases, the second mutation is 202A, but it can also be 968C or 680T (Table 4). The fact that African deficiency mutations of the G6PD A− type appear to occur only in the context of the 376G mutation of G6PD A+ suggested to us at one time that the primordial human G6PD may have been G6PD A+.[242,243] It is now clear on the basis of haplotype analysis that the A+ mutation is more recent in origin than the prototypal G6PD B.[244,245] A more attractive explanation for the association of the 376G mutation with other African deficiency mutations is provided by the finding of Town et al[246] that the 202A mutation produced by site-directed mutagenesis alone is not enough to produce enzyme deficiency; the 376G mutation, which ordinarily does not produce enzyme deficiency, is required. Thus, it is possible that the mutations at nt 202, 680, and 968 would have had no selective advantage against malaria when they occurred in a G6PD gene that did not have the 376G mutation. However, two mutations that have been found to produce hemolytic anemia when present together with the 376G mutation also result in deficiency when found alone. These are 542T[247] and 1159T.[248]

The data regarding the incidence of G6PD deficiency in various populations[223-225] can now begin to be viewed from the perspective of which mutations are actually found. The emerging data regarding the distribution of different mutations in various populations is summarized in Table 5. In general, mutations are limited to contiguous geographical areas or to areas where population migrations are well documented. Thus, G6PD A− has a broad distribution that includes all of Africa, Southern Europe, and wherever the slave trade brought Africans to the New World. G6PD Mediterranean is found in Southern Europe, throughout the middle East and in India, and G6PD Canton is found in Asia. An interesting exception to this rule is provided by G6PD Union^{1360T}. This mutation was described originally in the Philippines and has indeed been documented at the DNA

Table 5. Population Distribution of Common G6PD Mutations

Mutation	Population	Reference
Gaohe^{95G}; Gaozhou^{95G}	China	219, 249, 404
Aures^{143C}	Algeria	406
	Saudi Arabia	103
	Spain	247
Ube^{241T}; Konan^{241T}	Japan	411
A-$^{202A/376G}$*	Africa	245, 266, 436
	Italy	410, 412
	Spain	242, 247
	Canary Islands	219
	Mexico	408
"Chinese-4"^{392T}	China	336, 416
"Chinese-3"^{493G}	Philippines	249
Mahidol^{487A}	Southeast Asia	249, 417
	China/Taiwan	218, 336
Santamaria$^{376G/542T}$	Costa Rica	420
	Canary Islands	219
	Italy	412
Mediterranean^{563T}*	Italy	407, 412
	Sardinia	219, 421
	Greece	219
	Saudi Arabia	103, 335
	Iran	335
	Iraq	335
	Israel	335
	Egypt	335
	Jews, Kurdish	221
	Jews, Ashkenazi	409
Seattle^{844C}*	Italy	250
	Spain	247
	Sardinia	219
	Canary Islands	219
Viangchan^{871A}*	India	424
	China	219
	Laos	249, 250, 424
	Philippines	249, 250
A-$^{376G/968C}$	Africa	204
	Spain	242, 247
	Canary Islands	219
Kalyan^{949A1}	India	427
Chatham^{1003A}	Philippines	249
"Chinese-5"^{1024T}	China/Taiwan	336
Union^{1360T}*	Philippines/Laos	249, 250
	China	219, 336
	Japan	249
	Spain	247
	Italy	251
Canton^{1376T}*	China	219, 336, 434, 435
Kaiping^{1388G}	China	219, 336, 434
	Laos	250

* See Table 4 for additional designations for the same variant.

level among Filipinos in Hawaii.[249,250] Surprisingly, this variant has also been detected in Spain,[247] Italy,[251] and in the Vanuatu archipelago in the Southwestern Pacific.[252]

When mutations are as widely dispersed as is G6PD Union^{1360T}, the question arises of whether they represent recurrent, independent mutations at a susceptible site in the gene, on the one hand, or whether they have a single origin and have been spread through population flow. Study of other mutations in the G6PD gene that do not cause enzyme deficiency, but represent polymorphisms that together constitute various haplotypes, is a useful tool for the study of this question.

G6PD polymorphisms that do not cause enzyme deficiency. Although principal attention has been paid to mutations of the G6PD molecule that produce enzyme deficiency, and therefore, may cause anemia, other mutations in the gene have been of considerable interest in studies of populations and of genetic linkage. G6PD A+ is the polymorphism of this type that has been known for the longest period of time. Now recognized as a A→G mutation at cDNA nt 376, this mutation was first discovered because of the faster electrophoretic migration of the enzyme.[253] It was used by Linder and Gartler[254] to show that uterine myomas arose from single cell precursors, by our group to show that lymphomas have a single cell origin but that colon carcinoma may arise from many cells,[255] and subsequently by others to study the pathogenesis of many other neoplasms.[256-262]

Study of the DNA sequence has shown a number of additional polymorphic sites that are "silent" in the sense that they do not change the sequence of the protein. Among Africans, there is a polymorphism in intron 5 creating a *Pvu* II site[263] and at nucleotide 1116 of the coding region creating a *Pst* I site.[264] Intron 7 contains a C→T substitution in some Africans. A *Sca* I site can be created with a mismatched primer and the polymorphic site has been designated "*Sca*".[245] Intron 11 also contains a polymorphism, widespread in many populations, that produces an *Nla* III site.[265] Another polymorphism in the coding region that does not produce an amino acid substitution at nt 1311 is widespread in all populations. These polymorphic sites create haplotypes that have been useful in establishing the order in which the various mutations of the G6PD gene arose. The G6PD A$-^{202A/376G}$ mutation is of quite recent origin and may have had a single origin.[244,245,266] Based on the distance of these mutations from the G6PD A− mutation at nt 202 we have calculated that it is extremely unlikely that G6PD A− arose more than 80,000 years ago, although its origin might have been much more recent.[244] In contrast, G6PD Mediterranean^{563T} is found in the context of two different haplotypes. In most European patients with this mutation, a T is present at nt 1311, whereas on the Indian subcontinent, most subjects with this mutation have a C at nt 1311.[267,268] This finding is consistent with recurrent independent mutational events producing the G6PD Mediterranean^{563T} mutation in different populations, but it is also possible that this mutation is very old and that crossovers occurred in the gene. Similarly G6PD Jammu^{871A} and G6PD Viangchan^{871A} occur in different haplotypes and may have had separate origins.[265]

The nt 1311 is of greater potential value than the other polymorphic sites. Because this polymorphism is panethnic, it, together with the panethnic intron 11 site, can be used to investigate the origin of non-African mutations. Because it is a part of the mature mRNA, the 1311 mutation serves as a marker of gene expression. Nucleotide 1311 of the cDNA is normally a T. However, in some individuals it is a C. We found the mutant (C) genotype in 9/54 X-chromosomes from Europeans of mixed origins, 9/41 X-chromosomes of Ashkenazi Jewish subjects, 3/18 X-chromosomes of Sicilians, 5/20 African X-chromosomes and 9/20 Asian Indian X-chromosomes. In contrast, the mutation was found in only 3/59 Asian X-chromosomes and 3/30 Central/South American X-chromosomes.[268] Because it is in the coding region, one may assess expression of the gene by reverse transcribing cellular mRNA and examining the cDNA for the mutation. We have done this in the case of a patient with X-linked chronic granulomatous disease, establishing the clonal nature of the mutation[269] and it has also been adapted to study hematopoiesis in normal subjects and in a patient with polycythemia vera.[270]

G6PD Deficiency as a Balanced Polymorphism

When a gene that has some potential for decreasing fitness achieves a high frequency in some populations, it is necessary to assume that in those populations it also confers a survival advantage. Thus, a balance has been achieved between the advantage and the disadvantage conferred by a gene, and this is designated a balanced polymorphism. One of the most studied of such polymorphisms is the mutation for sickle Hb, and evidence from a variety of sources has led to the conclusion that the advantage conferred by this gene is resistance to falciparum malaria. The mortality caused by malaria in some parts of the world is so high that a large number of genetic traits that defend against this infection have evolved in mankind, and many polymorphisms affecting the RBC seem to have reached high frequencies for this reason.[271]

Malaria. The geographic distribution of G6PD deficiency led Motulsky,[272] Siniscalco et al,[273] Allison,[181] and Allison and Clyde[274] to suggest nearly 35 years ago that G6PD deficiency is also one of the polymorphisms that confers resistance to infection with falciparum malaria. The evidence for this, recently reviewed in detail by Greene,[275] comes from several types of studies:

(1) Epidemiologic investigations indicate that the highest gene frequencies are present among populations living in low-lying areas in which the incidence of malaria is high.[227,276] These relationships have been questioned,[227,277] and it has been suggested that an additional factor, perhaps oxidative stress,[275,278] may be required for G6PD deficiency to confer immunity to malaria. The malaria parasite appears to be sensitive to oxidative stress,[279-282] and it has been suggested that the eating of fava beans protects synergistically with G6PD deficiency against malaria,[275,282,283] but it is difficult to explain protection against malaria on this basis in sub-Sahara Africa where fava beans are not cultivated.

(2) Decreased parasitemia among patients with G6PD deficiency when compared with normal individuals was originally reported by Allison[181,274] and has been confirmed in a number of studies.[227,284,285] A number of negative studies have also been reported,[286,287] but are considered to be

flawed.[275] Although one study indicated that protection extended only to heterozygous females,[288] this conclusion has not been borne out in other investigations, and it seems likely that hemizygous males are also protected.[275] However, based on the now-disputed finding that it is heterozygotes that are resistant to malaria, an interesting explanation was devised. It was suggested that when deficient cells are parasitized that the parasite G6PD is eventually induced, but that this requires several cycles in deficient host cells. Heterozygotes, who have a mixture of normal and deficient cells would host the parasite in normal cells sufficiently often to prevent the induction of enzyme.[253,289] However, subsequent data from the same group of investigators indicated that in reality, the G6PD activity of the host cells did not influence the expression of parasite enzyme.[290]

(3) Studies in heterozygotes for G6PD deficiency, in whom two populations of RBCs coexist, show that more parasites are present in the cells with normal enzyme activity than in the deficient cells. In an elegant investigation of the number of parasites in the RBCs of patients heterozygous for G6PD deficiency, Luzzatto et al[291] showed that more parasites could be found in G6PD-sufficient than in G6PD-deficient cells.

(4) In vitro studies show that malaria parasites grow less well in G6PD-deficient than normal cells.[253,281,289,292]

Sickling. The coexistence of the gene for sickling and that for G6PD deficiency in the African population has led to many investigations regarding the possible relationships between these two disorders. In some studies, a positive association has been found between these genes,[293-298] and it was suggested that the gene for G6PD deficiency might confer an advantage on patients with sickle cell disease, prolonging their survival. However, it was shown that sibs of patient with sickle cell (SS) disease also had an equally high incidence of G6PD deficiency and suggested that concordance between these genes was not caused by a selective advantage, but rather by dilution of genes of African origin, so that individuals with many African genes would have a higher probability of carrying both of these defects than individuals in whom the proportion of African genes was lower.[299] Indeed, it has been shown that G6PD deficiency does not affect the clinical course of sickle disease,[300,301] neither increasing its severity as had been suggested[302] or decreasing it as had also been proposed.[294] Moreover, most studies of fairly homogeneous populations show the incidence of hemoglobin S and G6PD deficiency are quite independent.[303-307]

DIAGNOSIS

Detection of G6PD Deficiency

Before the underlying defect, G6PD deficiency, had been uncovered, two methods for detecting individuals sensitive to the hemolytic effect of primaquine had been developed, the Heinz body test[308] and the GSH stability test.[179] Although still occasionally used, these surrogate tests are obsolete and no longer have a role in the diagnosis of G6PD deficiency. Instead, quantitative assays or screening tests that detect severe deficiency should be used to diagnose the disorder.

Quantitation of G6PD activity in erythrocytes. The simplest type of quantitative assay measures the reduction of NADP to NADPH in the presence of glucose-6-P and hemolysate. In reality, this type of assay measures both G6PD and 6-phosphogluconate dehydrogenase (6-PGD) activity. In the reaction mixture, as in the cell, the immediate product of the G6PD reaction, 6-phosphogluconolactone is converted to 6-phosphogluconate which serves as substrate for the 6-PGD reaction. Thus, 2 moles of NADP are reduced for each mole of glucose-6-P consumed in the mixture. Although methods that measure G6PD activity independently of 6-PGD deficiency have been available for many years,[309-312] such methods have little additional utility in diagnosing the deficiency state, because 6-PGD does not usually limit the rate of the reaction, particularly in G6PD-deficient individuals.

Screening for G6PD deficiency. In hemizygous males who are not undergoing hemolysis, as will be found in population surveys, semi-quantitative or nonquantitative screening methods are entirely adequate. Dye reduction tests, first introduced by Motulsky and Campbell-Kraut[313] as the brilliant cresyl blue decolorization test, have been widely used. Other receptors for the electrons from NADPH generated in the G6PD and 6-PGD reactions include methylene blue,[314,315] MTT tetrazolium,[313] and methemoglobin.[316] A test in which protection against denaturation of Hb under oxidative stress serves as an endpoint has also been developed.[39,317] Although all of these tests are still sometimes used, particularly in population surveys, they have largely been replaced by the fluorescent spot test, in which the generation of NADPH is detected directly visually under ultraviolet light.[39,317-321]

Detection of G6PD deficiency in patients undergoing hemolysis. While the diagnosis of deficient males ordinarily poses no special difficulties, the same cannot be written about the detection of G6PD deficiency in patients with some of the milder G6PD-deficient variants (class 3) undergoing a hemolytic episode. Because the older members of the RBC population are selectively removed in patients with variants such as G6PD A−,[14] leaving the younger cells with near-normal activity in the circulation,[15] a screening test may give quite normal results, at least for a week or two after the hemolytic episode. The same problem in diagnosis does not exist in the case of severe (class 2) variants because in these variants, even the very young cells are severely enzyme deficient.[15,16]

Several different approaches may be used to diagnose patients who have just undergone hemolysis. The simplest is merely to wait for a week or two or to perform family studies. Alternatively, one may deplete the sample being studied of reticulocytes by centrifugation. The denser cells, although not truly old as has sometimes been believed, are depleted of very young RBCs.[322] Accordingly, it has been found that even during hemolysis, the dense fraction of cells is G6PD deficient.[323,324] Another approach is to compare the activity of G6PD with that of another age-dependent RBC enzyme such as hexokinase or glutamic oxaloacetic transaminase.[325] This approach has been used also to detect the G6PD A− genotype in patients with sickle cell disease, in which the mean RBC age is greatly decreased.[299]

The most powerful approach for establishing the diagnosis

in the context of hemolysis is analysis of genomic DNA obtained from circulating leukocytes (see below). Neither the presence of young erythrocytes nor, for that matter, of transfused cells confounds the results obtained from such an analysis.

Heterozygote detection. Detection of heterozygotes for G6PD deficiency poses special problems. Because of X-inactivation, heterozygotes have two RBC populations.[185,326] One of these populations consists of normal RBCs and the other of RBCs that are as deficient as those of a hemizygous male with the same deficient variant. On the average, half of the cells are normal and half are deficient. However, in some heterozygous women most of the cells are deficient; in others most are normal. The result of assaying the activity of enzyme per gram Hb reflects the proportion of normal and abnormal cells in the individual being studied, and some heterozygous women will have normal RBC enzyme activity whereas others will be grossly deficient in enzyme activity. Thus, the usual RBC enzyme activity measurements cannot be relied upon for the detection of heterozygotes.

A more acceptable approach is to use techniques in which each RBC acts as an independent metabolic unit. Methemoglobin reduction can be used for this purpose, but only if the dye that links methemoglobin reduction to NADP reduction does not result in cell-to-cell interaction. Nile blue sulfate can be used for this purpose, but not methylene blue.[327-329] Reduction of a tetrazolium dye can also serve as an endpoint.[330-332] Although such methods may be able to identify heterozygotes with as few as 5% to 10% normal or abnormal cells, some heterozygotes will escape detection because virtually no normal or no abnormal cells are present in the circulation.

The most accurate method for heterozygote detection is to detect the mutation in genomic DNA. Although X-inactivation may alter the methylation pattern on the inactive X-chromosome[201,333] and prevent transcription of the inactive gene,[269] it does not prevent the detection of the difference in the nucleotide sequence of the gene. Thus, heterozygote detection by DNA analysis is entirely reliable, provided that the mutation to be detected is known.

Identification of G6PD variants. It became apparent early in the study of G6PD deficiency that there were differences in the characteristics of the residual enzyme in different deficient individuals. Fortunately, a WHO expert committee standardized the methods for the purification and characterization of G6PD variants in 1967,[13] and most investigators subsequently used the same techniques for the examination of different variants. The technology that was agreed upon consists of partially purifying the enzyme by absorption on and elution from diethylaminoethyl cellulose, followed by ammonium sulfate fractionation. The partially purified enzyme is then examined kinetically, electrophoretically, and by measuring its thermal stability. This technology proved to be useful in obtaining a general impression of the degree of diversity of G6PD in various populations. However, the volumes of blood required were large, and it was often difficult to be certain whether relatively minor differences in properties were caused by the existence of new variants or whether the observed variation was methodologic. As pointed out above, 442 variants have been claimed to be distinct. Variants that were believed to be likely to be different, specifically, G6PD Cornell and Chicago, were shown to be from members of the same extended family.[334]

The development of a number of PCR-based methods for the detection of known mutations in G6PD has made it possible to detect G6PD deficiency and to identify the specific mutation responsible with relative ease. The advantage of the use of this type of technology is that DNA samples are much more stable than the enzyme in blood samples, and that very small volumes suffice for diagnosis. Methods of detection include the use of restriction endonucleases to cleave naturally occurring restriction sites[204] or restriction sites produced by making mismatched oligonucleotides[335,336] and allele-specific oligonucleotide hybridization.[249] These methods are sufficiently facile for population screening and require so small a sample that they can be used for prenatal diagnosis.[337]

TREATMENT

When hemolytic episodes occur in G6PD-deficient individuals, the inciting agent, drug or infection, should be removed whenever possible. However, in patients who have class 3 variants such as G6PD A−, it may be possible to continue essential drug therapy with careful monitoring of the blood count. Blood transfusion is only occasionally required to support patients who have undergone severe hemolytic episodes, usually in patients with favism.

It has been suggested[338] that attacks of favism may be ameliorated by the administration of desferrioxamine. In one study,[339] patients with favism who received a single 500-mg dose of desferrioxamine and packed RBC transfusions had a shorter duration of hemoglobinuria, greater rise in Hb level and more rapid drop in reticulocyte count than control patients who received packed cells alone. However, it was not clear that both groups received the same volume of transfusion.

To permit NADPH to be produced by a different route, xylitol administration has also been proposed as a way to prevent or treat hemolysis of G6PD deficiency.[340] Clinical studies in which two severely G6PD-deficient volunteers were pretreated with 10 g xylitol per day and then given primaquine and 20 g xylitol per day showed no protection against hemolysis.[341]

It has been suggested that vitamin E, by virtue of its antioxidant effect, might protect against chronic hemolysis in G6PD deficiency causing chronic hemolytic anemia. Some studies have shown a favorable response to this vitamin[141,342-344]; others have not.[345,346]

The most dangerous consequence of G6PD deficiency is neonatal icterus. Kernicterus has been documented repeatedly in populations in which class 2 variants are common,[100-103,107,347-352] and it has been pointed out this is an important preventable form of mental retardation.[108] Phototherapy[111,353,354] has been used to reduce bilirubin levels, and phenobarbital has been used prophylactically with some success.[104] Agar, given to reduce bilirubin reabsorption, was found to be ineffective.[355] Exchange transfusion is required if the bilirubin exceeds 20 mg/dL,[111] but G6PD-deficient blood should not be used for this purpose.

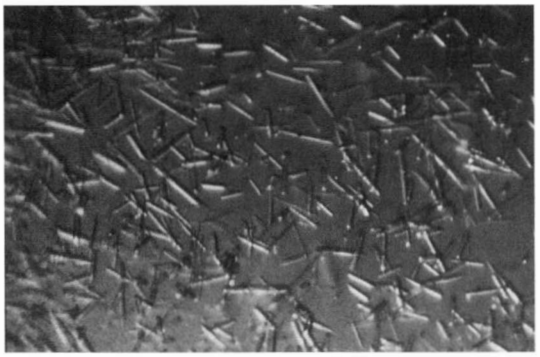

Fig 2. Crystals of human RBC G6PD (magnification × 120) (Courtesy of Drs Enrico A. Stura, Jairo Arévalo, and Ian A. Wilson, The Scripps Research Institute. Original magnification in Kodachrome × 60).

Future Prospects

It has now been almost 40 years since G6PD deficiency was identified as the cause of primaquine sensitivity, and many thousands of papers documenting clinical events, population distribution, biochemical characteristics, and molecular biology have been published. Are there any questions that remain to be answered? The natural occurrence of many mutations and documentation of their biochemical effects is a rich resource for furthering our understanding of structure-function relationships of enzymes. For this reason, both our group and Luzzatto's, working together with crystallographers, have invested considerable effort in attempting to solve the three-dimensional structure of the enzyme. Although we have succeeded in crystallizing the enzyme (Fig 2), it is apparently too inhomogeneous to allow useful information to be obtained. Thus, our understanding of the functional sites has been limited to inferences drawn from the location of mutations that have well-defined biochemical defects. Answers to other questions are needed as well. We would like to understand the difference between individuals who develop favism and those who do not. Are divicine and isouramil really the active principles of the beans? What are the actual mechanisms of drug-induced and infection-induced hemolysis? What is the mechanism of neonatal icterus? Why is it the RBCs that are primarily affected in the deficiency state?

It is of the nature of science that as we solve problems new problems arise. G6PD deficiency is no exception to this rule.

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