THE YALE JOURNAL OF BIOLOGY AND MEDICINE 52 (1979), 169-179

Glucose-6-Phosphate Dehydrogenase Deficiency and Infection: A Study of Hospitalized Patients in Iran

MARCIA CLARK, M.D.,[1] AND RICHARD K. ROOT, M.D.

Infectious Disease Section, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

Received July 14, 1978

The Mediterranean variant of glucose-6-phosphate dehydrogenase (G6PD) is functionally deficient and found in a variety of cell types of affected individuals, including both erythocytes and neutrophils. To determine if the presence of this sex-linked gene is associated to any degree with the occurrence of severe bacterial infection, a study of hospitalized male patients in Iran was undertaken. As determined by erythrocyte assay, allele prevalence in male patients with infection was 22% vs. 12% in a patient group matched for the absence of other risk factors for infection and 6% in a second group who had additional risk factors for infection. When the control and patient groups were considered together the difference between the frequency of G6PD deficiency (10.2%) was significantly different from that found in the infected patients ($p < .05$). Furthermore the mean age of infected patients with G6PD deficiency was significantly less than that of infected patients without G6PD deficiency or non-infected control groups. These data suggest that host defenses may be altered in G6PD deficiency so that bacterial infections are more severe. Alternatively, G6PD deficiency and infection might represent concomittant risk factors which lead to hospitalization during bacterial infection. Potential mechanisms by which host defenses might be altered in G6PD deficiency are discussed.

Glucose-6-phosphate dehydrogenase (G6PD) is a cytoplasmic enzyme which catalyzes the conversion of glucose-6-phosphate to 6-phosphogluconolactone. This reaction which requries $NADP^+$ as a cofactor, is the rate limiting step in the operation of the so-called pentose shunt, an enzymatic system found in almost all human cell-types. Besides the formation of five-carbon sugars, the products of pentose-shunt activity include NADPH and CO_2 [1]. In erythrocytes, pentose-shunt activity is linked to a recycling of oxidized to reduced glutathione, through the provision of NADPH; and plays an important role in the antioxidant defenses of these cells [2]. G6PD activity is a sex-linked trait with a number of variant types and isoenzymes described, some of which are pathogenetically important because of decreased activity. G6PD Mediterranean is the name given to an enzyme type found in certain percentages of Mediterranean, Middle Eastern and Far Eastern population groups. In contrast to other G6PD types, it is unique both for its markedly reduced activity and its wide distribution among a variety of cells, including granulocytes [1,3,4].

Individuals with G6PD Mediterranean may experience severe hemolysis when exposed to certain oxidants or the oxidant stress of infection [5]. Furthermore, severe

Supported in part by USPHS Grant AI 13251 (Dr. Root).

[1]Current address: Children's Hospital of Philadelphia, Civic Center Boulevard, Philadelphia, PA 19104

Address reprint requests to: Richard K. Root, M.D., Infectious Disease Section, Department of Internal Medicine, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510

0044-0086/79/5202-0169 $01.10

deficiencies of granulocyte G6PD activity (< 5%) may be associated with repetitive bacterial infections and an inability to kill catalase-positive microorganisms [6–8]. The mechanism for this microbicidal defect appears to lie in a failure to form adequate amounts of superoxide and H_2O_2 from molecular oxygen during phagocytosis, through the action of an oxidase which utlizes NADPH as a substrate [9]. Such severe deficiencies are unusual, however, and in most studies the degree of granulocyte G6PD activity in G6PD Mediterranean averages between 25 to 33% of normal [3,4]. Even so it is possible that such neutrophils may be less able to withstand oxidant stresses and to detoxify H_2O_2 formed during phagocytosis because of depleted intracellular GSH stores [9]. Evidence exists that depletion of intracellular GSH in granulocytes may impair critical events in normal motility responses such as the assembly of microtubules [10,11] and the H_2O_2 accumulation may be a mechanism of cell death during phagocytosis [12]. With these points in mind an increased susceptibility to bacterial infection in patients with Mediterranean G6PD might occur either because of intravascular hemolysis leading to a functional blockade of the reticuloendothelial system as suggested by Kaye et al. [13] or because of abnormal leukocyte function or both.

Although several individual patients with G6PD Mediterranean have been described whose susceptibility to infection could be traced directly to defective neutrophil bactericidal function, no information is available as to the relevance of the other postulated mechanisms. Furthermore, data from population studies on the relative incidence and prevalence of bacterial infections as a function of G6PD activity is scanty and incomplete. As a prelude to further *in vitro* studies and in an attempt to determine if the presence of Mediterranean G6PD might alter susceptibility to infections, a study of hospitalized patients in Shiraz, Iran, was undertaken.

MATERIALS AND METHODS

Performance Site and Initial Patient Selection

This study was carried out over a three-month period (May–July 1976) in Shiraz, Iran, at Nemazee and Saadi Hospitals, two teaching hospitals affiliated with Pahlavi University Medical School. All subjects were Iranian males and all, except one, inpatients at one of these hospitals. Males were chosen since they would be either G6PD deficient or normal.

Collection of Demographic Data

Approximately three times per week charts were reviewed of all adult male patients in Nemazee Hospital and from the medical, orthopedic, and neurosurgical wards in Saadi Hospital. Charts of male pediatric patients were also reviewed during the last month of the study. The data collected included age, place of origin, history of present illness, past medical history, family history, physical examination findings, laboratory data, procedures performed, and hospital course. When necessary, patient information was also obtained from responsible medical personnel. Complete records of all the demographic parameters could be obtained on over 95% of the patients by these means.

Collection of Data Regarding Infection

The diagnosis of infection was established by one or more of the following methods: cultures, specific antibody titers, biopsies, X-rays, examination of inflammatory effusions and, finally, response to therapy with specific antimicrobials.

Depending upon the specificity of the findings used to establish the etiologic agent, infected patients were placed into two groups as described below.

Patient Exclusions

As far as possible all individuals with systemic diseases other than G6PD deficiency or therapy which might predispose in some way to bacterial infection were excluded from study. Diagnoses in the excluded group included patients with malignancy, diabetes mellitus, cirrhosis, renal failure, cardiac failure, sickle cell anemia, thalassemia, malaria, echinococchosis, viral infections, tetanus, open trauma, renal stones, and vasculitis. Patients receiving glucocorticoids or in whom no diagnosis of a specific disease could be made were also excluded. When patients with any of these conditions were studied before a precise diagnosis was made, they were placed into a separate group for data analysis as noted below.

Definition of Infected Patient Groups

All patients with bacterial infections and no known predisposing reason for infections other than possible G6PD deficiency were placed into the infected group. In cases where the etiologic agent was definitely established by culture results, diagnostic antibody titers, or biopsy findings the patients were categorized as "Class 1." Patients in whom a bacterial etiology for infection was highly suspected but not definitely proven were placed in "Class 2." Class 2 patients included those with a combination of X-rays consistent with pneumonia or tuberculosis, inflammatory responses in body fluids or biopsies consistent with pyogenic or tuberculous infection, clinical symptoms characteristic of bacterial infection, and a response to antimicrobial therapy. One patient in the infected group was seen at the Nemazee Outpatient Clinic. Brucella agglutinin titers were diagnostic of infection with this organism and it was elected to treat him at home rather than in the hospital.

Definition of Control Groups

Those male patients free of diseases known to be associated with infection or G6PD deficiency were designated as control group "A." Control group "B" patients consisted of individuals without defined infection who were tested before a definitive clinical diagnosis was available. All of these patients had a variety of potentially predisposing factors to infection, or syndromes which mimic bacterial infections in some of their features (e.g., fever).

G6PD Assays

Measurement of erythrocyte G6PD activity was carried out as follows: for each assay, approximately 5 cc of blood was drawn into a syringe, transferred immediately to a Vacutainer tube containing EDTA, and mixed well. Bloods were refrigerated at 4°C within 15 minutes and were tested within three days with the semiquantitative method developed by Sigma (Technical Bulletin No. 400). Kit instructions were followed exactly, including appropriate compensation for the degree of anemia present. In this assay, erythrocytes are lysed by water to release G6PD. This solution is then added to glucose-6-phosphate and NADP in the presence of phenazine methosulfate, an electron carrier, and dichlorophenol indophenol, a blue dye. The NADPH formed during the oxidation of glucose-6-phosphate to 6-phosphogluconate reduces the dye to a colorless form, and the rate of the reaction can be followed visually. The tubes are observed for a six-hour period. For a minority of patients the quantitative test for G6PD activity performed in the Nemazee Hospital Laboratory

(Brilliant Cresyl Blue Reduction, Dade, Miami, CA) was used. In these cases, only samples with 0% activity were considered deficient.

Grouping of Data and Statistical Analysis

Statistical significance of differences in rates of G6PD deficiency were determined by the chi-square method of analysis. Infected patients were compared with control "A" and control "A" plus control "B." No separate comparisons with control "B" were made, because of the small number of subjects. Subgroups of patients matched exactly for age and origin were analyzed in a similar way. Those infected patients in whom an etiologic agent was established were divided according to whether the agent contained catalase or was catalase negative. The catalase positive group was compared with controls, but the catalase negative group was too small to permit statistical analysis. The unpaired "*t*" test was used to analyze the mean age difference between the G6PD normal and the G6PD deficient infected groups. With both the chi-square and the unpaired "*t*" test, $p < .05$ was considered statistically significant.

RESULTS

Assay Validity

Before conducting the studies in Iran, assays were run at Yale University School of Medicine using blood samples tested quantitatively by the Yale–New Haven Hospital laboratories. The age of the samples ranged from two hours to eleven days. Samples of all ages with normal G6PD activity decolorized within one hour, and samples with 10 percent activity decolorized in two to two and a half hours, consistent with data obtained by Sigma.

In Iran, an effort was made to study all infected patients as soon as possible after admission, usually within a few days. It was not always feasible to carry out the assays when no medications were being given; however, a complete list of drugs that each patient was receiving was compiled, and no agents that might have affected the assay were present in the study group. Fourteen of our seventeen abnormal samples had not decolorized at 6 hours, indicating very severe deficiency. Two of the remaining three took 3 hours but when repeated took 4 hours or more, and the third took 4½ hours but could not be repeated. Of the fourteen that took more than 6 hours, 5 were randomly repeated and all confirmed the original result; in two cases the assay was performed within 2 hours of the time the blood was drawn. Three of the normal assays were repeated and confirmed.

Patient Characteristics

The demographic characteristics of all patients are presented in Table 1. The average age of the 55 infected patients was 31 years; the G6PD normal group differed substantially from the G6PD deficient group, 34 years compared to 22. This difference was statistically significant ($.001 < p < .005$). There were 65 control "A" patients, with an average age of 34 years, and 33 control "B" patients, with an average age of 38 years. In these two groups there was no difference between the proportions of G6PD normal and G6PD deficient patients. The distribution between those from villages and from major cities was relatively even, although a somewhat greater proportion of the control "A" group came from the cities. Of the city patients, a total of seven came from places other than Shiraz (three infected patients and three control "B" patients, one each from Yazd, Teheran, and Mashad, and one control "A" patient from Yazd). It seems reasonable to assume that villagers are less likely to

TABLE 1
Patient Demographic Data

Category		Number of Patients	Average Age (Range)	Origin			
				Village	City[a]	Nomad	Not Known
Infected	G6PD nl	43	34 (8-85)	22	14	1	6
	G6PD def	12	22 (11-35)	8	3	0	1
	Total	55	31 (8-85)	30	17	1	7
Control "A"	G6PD nl	57	34 (14-70)	28	28	0	1
	G6PD def	8	37 (22-55)	6	1	1	0
	Total	65	34 (14-70)	34	29	1	1
Control "B"	G6PD nl	31	38 (15-80)	18	10	0	3
	G6PD def	2	39 (18-60)	2	0	0	0
	Total	33	38 (15-80)	20	10	0	3

[a] Shiraz, Teheran, Isfahan, and Mashad

travel, and that therefore an even smaller percentage is from outside the Shiraz area.

The criteria by which infections were established are listed in Table 2, and the actual diagnosis in Table 3. Table 4 contains the diagnosis of control "A" and control "B," respectively. Some of the patients had a history of a disease other than that for which they were admitted to the hospital. Of the infected patients, three had a past history of typhoid (the present illnesses were two with pneumonia and one with osteomyelitis), one had psoriasis (shigellosis), and one had hypertension (meningitis).

TABLE 2
Diagnostic Criteria in Infected Patients

Class I:	Diagnosis	Criterion for Diagnosis[a]
	Pneumococcal infection	Culture
	Staphylococcal sepsis	Culture
	Streptococcal meningitis	Culture
	Shigellosis	Culture
	Anthrax	Culture
	Brucellosis	Titer
	Typhoid	Titer
	Tuberculosis	Biopsy
	Actinomyces Israelii abscess	Biopsy
Class II:	**Diagnosis**	**Criteria for Diagnosis[a]**
	Pneumonia	Chest X-ray and response to antibiotics
	Meningitis	Cerebrospinal fluid findings and response to antibiotics
	Osteomyelitis	X-ray or biopsy
	Tuberculosis	Chest X-ray
	Erysipelas	Response to antibiotics
	Brain abscess	Cerebrospinal fluid findings plus air fluid level on skull X-rays
	Pyopneumothorax	Pus in pleural fluid

[a] In all cases, clinical symptoms were also compatible

TABLE 3
List of Infected Patients by Diagnosis

Diagnosis	Number of Patients	Number Deficient
Osteomyelitis	12	2
Tuberculosis	9	1
Pneumonia[a]	8	4
Brucellosis	6	2
Staphylococcal septicemia	3	2
Meningitis[b]	3	1
Typhoid	3	0
Anthrax	3	0
Shigellosis	3	0
Erysipelas	1	0
Pyelonephritis	1	0
Pyopneumothorax	1	0
Brain abscess	1	0
Extradural abscess	1	0
	55	12

[a] In 2 cases, one of which was G6PD deficient, the etiologic agent was determined by culture to be pneumococcus.
[b] In 1 case, which was G6PD normal, the etiologic agent was determined by culture to be hemolytic streptococcus.

Of the control "A" patients, one had had typhoid (snake bite), one had had malaria (upper gastrointestinal tract bleed), and one had had an ulcer (low back pain); of control "B" patients, one had rheumatoid arthritis (and was on steroid therapy) and one had had smallpox (diagnosis of present illness not made).

The results of the G6PD assays are in Table 5. Twenty-two percent of the infected patients were G6PD deficient, compared to twelve percent of control "A" and six percent of control "B" (Table 5a). Tables 5b, 5c, and 5d show the rates of G6PD deficiency in three subgroups, one with matched ages, one with matched origins (villagers only), and one selected on the basis of whether the etiologic agent was catalase positive or catalase negative. Matching for age was important from two aspects: older patients might have a lower frequency of G6PD deficiency if the gene causes an increase in mortality rates and older patients have a naturally higher rate of infection for a variety of reasons. Matching for origin was important to account for genetic differences in rates of G6PD deficiency, and genetic and environmental differences in rates of infection. We looked at whether infections were caused by catalase positive or catalase negative organisms, because of the previously cited work showing that G6PD deficient leukocytes may be similar to leukocytes obtained from patients with chronic granulomatous disease in having impaired killing of catalase positive organisms [5–7].

For Tables 5a, 5b, and 5c the differences in rates of G6PD deficiency between the infected group and control "A" were analyzed by the chi-square method, and in all cases the differences were found not to be statistically significant ($p > .10$). When comparisons were made between each infected group and control "A" plus control "B" patients, the value for differences between prevalence rate for G6PD deficiency was significant ($< .05$) when all patients were considered or the groups were matched for age. No separate comparisons with control "B" were made, owing to the small number of subjects. In Table 5d, the group infected with catalase positive organisms was compared with all control "B" patients. The differences were not statistically

significant ($p > .10$). The catalase negative group had no G6PD deficiency, but statistical analysis was not carried out because of the small size of the group.

Mortality data were collected but are incomplete because it was not possible to follow patients remaining in hospitals after termination of the study. As far as is known, none of the 12 G6PD deficient infected patients and 2 of the 43 G6PD normal infected patients expired. There was no mortality in the control "A" group of 65 patients; in control "B," one of the 2 G6PD deficient and 3 of the 31 G6PD normal patients failed to survive.

DISCUSSION

The frequency of G6PD deficiency in Iran has been studied by a number of other investigators (refer to Table 6), and our results are in rough agreement. We did not

TABLE 4
Diagnosis in Control Patients

Diagnosis	Number of Patients	Number Deficient
	Control A	
Closed trauma	25	4
Upper gastrointestinal hemorrhage[a]	11	0
Disc herniation	10	2
Low back pain	4	1
Inguinal hernia	3	0
Minor congenital defect	3	0
Snake bite	3	1
Poisoning	3	0
Myocardial infarction	2	0
Burn contracture	1	0
	65	8
	Control B	
Malignancy	6	1
Pneumonia[b]	4	1
No diagnosis	4	0
Viral infection	3	0
Steroid therapy[c]	3	0
Open trauma	2	0
Diabetes mellitus	2	0
Thalassemia	1	0
Sickle cell anemia	1	0
Chronic renal failure	1	0
Chronic heart failure	1	0
Cirrhosis	1	0
Rheumatic heart disease	1	0
Tetanus	1	0
Renal stones	1	0
Opium abuse	1	0
	33	2

[a]Malignancy ruled out.
[b]Underlying causes (malignancy, hydatid cyst, TB) not ruled out.
[c]For rheumatoid arthritis, vasculitis of unknown etiology, and Henoch-Schonlein purpura.

TABLE 5
Comparisons of G6PD Deficiency Rates*

	Category	Number of Patients	Number Deficient	% Deficient
a. All Patients:	Infected	55	12	22
	Control "A"	65	8	12
	Control "B"	33	2	6

	Category	Number of Patients	Number Villagers	Number Deficient	% Deficient
b. Matched for Average Age: (31 years)	Infected	55	30 (55%)	12	22
	Control "A"	59	31 (59%)	7	12
	Control "B"	27	18 (67%)	2	7

	Category	Number of Patients	Average Age	Number Deficient	% Deficient
c. Matched for Origin: (Villagers Only)	Infected	30	27	8	27
	Control "A"	34	35	6	18
	Control "B"	20	36	2	10

	Category	Number of Patients	Average Age	Number Deficient	% Deficient
d. By Etiologic Agent (Infected, Class 1 only):	Catalase +	22	31	5	23
	Catalase -	4	50	0	0

Catalase +: Staphylococcus, Shigella, Salmonella, Brucella, Anthrax, *Mycobacterium tuberculosis*
Catalase -: Pneumococcus, Streptococcus, Actinomyces israelii
*When infected patients were compared to Control "A" patients the prevalence of G6PD deficiency was not significantly different by χ^2 analysis for all patients and groups matched for age and origin. When *both* Control "A" and "B" patients were collectively compared to infected patients p values for G6PD deficiency noted were: $<.05$ (all patients); $<.05$ (age matched); $= .10$ (origin-matched).

TABLE 6
G6PD Deficiency in Iranian Males, Published Studies

Study	% Deficient	Total Number Subjects	Subject Characteristics	Geographical Origin	Religion
Bowman 1959 [14]	9.8	358	Hospital staff	275 from Shiraz, others scattered	Moslem
Beaconsfield 1968 [15]	2.5			Yazd	Moslem
	25	192		Caspian littoral area	Moslem
	19-25			Kermanshah	Moslem
	9			Isfahan	Moslem
Hedayat 1969 [16]	7	142	Blood donors	Oman littoral area	
	9.9	557	and	Teheran	Moslem
	12	108	hospital staff	Teheran	Jewish
Frischer 1973 [17]	9.8	409			

A blank space signifies that the information was not available.

have enough geographic distribution to confirm or refute Beaconsfield's [15] finding of a higher incidence in previously malaria-infected areas. For the purpose of comparison it is noteworthy that our patient group most closely resembles that reported by Bowman for Shiraz [14].

Although the rates of G6PD deficiency were greater in infected than in control groups, the differences were not significant when the control group was matched as closely as possible for age, origin, and underlying diseases. When we included a secondary control group with a variety of conditions that were not present in the infected groups, the differences reached significance (p as low as $.01 < p < .05$, in patients matched exactly for age). However, the secondary control group included patients whose susceptibility to infection might have been increased due to disease (other than G6PD deficiency) or therapy; thus it was not strictly comparable with the infected patient group. While it is noteworthy that none of these patients had infections at the time of study, the prevalence of G6PD deficiency in control group "B" was almost identical to control group "A." Nevertheless it could be argued that an artificially low rate of G6PD deficiency in control "B" could occur if the combination of G6PD deficiency and infection had led to an increased mortality in this group before hospitalization. The same bias could occur if patients with G6PD deficiency are less liable to develop the types of disorders present in control "B." Either of these could explain why the differences in rate of G6PD deficiency between the infected and control groups increase when the secondary control group is included, rather than a specific effect of G6PD deficiency on host defenses against infection.

As noted, studies have shown that some G6PD deficient individuals are more susceptible to infection only by catalase positive organisms [5–7]. Although the prevalence of G6PD deficiency in patients infected with catalase positive organisms was 22.7% as opposed to zero in those infected with catalase negative species, the number of cases was too small to permit meaningful statistical analysis.

The average age of G6PD deficient patients with infection was 22 years; whereas that of G6PD normal infected patients was 34 years. This was a highly significant difference when analyzed by unpaired t-test ($p < .001 < .005$). One interpretation of this observation is that the combination of G6PD deficiency and infection leads to hospitalization at an earlier age than infection alone. This is consistent with the hypothesis that G6PD deficient patients, once infected, have a more severe clinical course. Data on mortality rates would be useful in further testing of this hypothesis, but our data are insufficient for this purpose.

It is important to point out some of the limitations imposed by a study of this type. First, the number of patients sampled was relatively small, and conceivably some of the observed trends might become significant only in a large population study. Second, we were not able to measure leukocyte G6PD levels, which would have made our study more precise. Exact data on leukocyte G6PD activity would be particularly relevant in establishing the clinical significance of defective pentose phosphate metabolism in these cells. Third, a lack of optimal facilities and culturing techniques within the particular hospitals prevented us from establishing every diagnosis of infectious disease by culture, and sampling error might have been involved in those that were. Fourth, it was not possible for us to document fully previous antibiotic therapy, before hospitalization. Such treatment could be important in altering the course of infectious diseases thereby affecting hospitalization rates. Fifth, by selecting mainly adult patients, we automatically minimized the chances of detecting very

serious effects of G6PD deficiency on host resistance, which could result in early mortality in childhood.

Finally, by selecting only hospitalized patients for study no information is gained on the incidence of infection in G6PD deficient patients. Specifically, ongoing hemolysis caused by infection or its treatment can lead to hospital admissions. By concentrating only on patients with infections severe enough to result in hospitalization, a true picture of a population's susceptibility to infection is not obtained. Rather, one has only an estimate of the prevalence of serious infections, and this estimate does not differentiate between infections made more severe by G6PD deficiency (with or without hemolysis) and the reverse. Close monitoring of hemolytic parameters before hospitalization would be required to determine whether this is a source of bias, as well as perhaps producing information on the relationship of hemolysis and infection; it would also provide a more accurate index of the *incidence* of infection in normal and G6PD deficient subjects.

Another population study of the relationship of G6PD deficiency and infection has been published by Lampe et al. [18]. They compared rates of G6PD deficiency in hospitalized Thai children with *S. typhi, H. influenza B, pneumococcal*, staphylococcal, and tuberculous infections with outpatient controls. Taking only male patients, their data show a difference in rate of G6PD deficiency between the infected group and the controls approaching significance ($p = .05$), a finding rather similar to ours. Their criteria for diagnosis for infectious disease were more rigorous than ours, but their definition of G6PD deficiency is vague, and it is not clear how well the patients and controls were matched for exact age and origin. Furthermore, like our study, their method of patient selection precludes an estimate of the relative incidence rates for infection in normal and G6PD deficient subjects.

Thus, while we can offer no final conclusions regarding the true relationship of G6PD deficiency and the incidence of bacterial infections, a reasonable interpretation of data from these studies is that the two conditions do have meaningful interactions. A thorough prospective analysis of large groups would be required to pick up changes in infection incidence rates as well as severity, and to distinguish among infections with different types of organisms. Such a project would be potentially useful in providing additional knowledge of host defense mechanisms, and may be clinically important for the millions of people with deficiency of this key intracellular enzyme.

ACKNOWLEDGEMENTS

The authors are deeply indebted to Drs. Abdolghader Molavi and Faramarz Ismail-Beigi of Shiraz University, Shiraz, Iran, without whose expert assistance and support this study could never have been undertaken and successfully completed.

REFERENCES

1. Stanbury JB, Wyngaarden JB, Fredericksen DS: The Metabolic Basis of Inherited Disease, 3rd ed. New York, McGraw-Hill, 1972
2. Beutler E: Abnormalities of the Hexose Monophosphate Shunt. Sem Hem 8:311, 1971
3. Marks PA, Gros RT: Erythrocyte G6PD Deficiency: Evidence of Differences Between Negroes and Caucasians with Respect to This Genetically Determined Trait. J Clin Invest 38:2253, 1953
4. Ramot B, Fisher S, Szeinberg A, et al: A Study of Subjects with Erythrocyte G6PD Deficiency. II. Investigation of Leukocyte Enzymes. J Clin Invest 38:2234, 1959
5. Williams WJ, Beutler E, Erslev AJ, et al: Hematology. New York. McGraw-Hill, 1972
6. Baehner RL, Johnston RB, Jr, Nathan DG: Comparative Study of the Metabolic and Bactericidal Characteristics of Severely G6PD Deficient Polymorphonuclear Leukocytes and Leukocytes from Children with Chronic Granulomatous Disease. RES 12:150, 1972

7. Cooper MR, DeChatelet LR, McCall CE, et al: Complete Deficiency of Leukocyte G6PD with Defective Bactericidal Activity, J. Clin Invest 51:769, 1972
8. Gray GR, Klebanoff SJ, Stamatoyannopoulos G, et al: Neutrophil Dysfunction, Chronic Granulomatous Disease, and Non-Spherocytic Haemolytic Anaemia caused by Complete Deficiency of G6PD. Lancet 2:530, 1973
9. Babior BM: Oxygen-dependent microbial killing by phagocytes. N Engl J Med 13:659-668; 721-725, 1978
10. Oliver JM, Albertini DF, Berlin RD: Effects of glutathione oxidizing agents on microtubule assembly and microtubule-dependent surface properties of human neutrophils. J Cell Biol 71:921-932, 1976
11. Chernoff D, Malech HL, Root RK: Inhibitory effect of H_2O_2 on human polymorphonuclear leukocyte chemotaxis and random migration. Clin Res 25:474a, 1977
12. Salin ML, McCord JM: Free radicals and inflammation: protection of phagocytosing leukocytes by superoxide dismutase. J Clin Invest 56:1319, 1975
13. Kaye D, Gill F, Hook E: Factors Influencing Host Resistance to Salmonella Infections: The Effects of Hemolysis and Erythrophagocytosis. Am J Med 254:205, 1967
14. Bowman JE, Walker DG: Glutathione Stability of the Erythrocytes in Iranians. Nature 184:1325, 1959
15. Beaconsfield P: G6PD Deficiency and Physiopathologic Processes. N Engl J Med 278:914, 1968
16. Hedayat SH, Amirshahy P, Khademy B: Frequency of G6PD Deficiency Among Some Iranian Ethnic Groups. Trop Geogr Med 19:163, 1969
17. Frischer H, Bowman JE, Carson PE, et al: Erythrocytic Glutathione Reductase, Glucose-6-Phosphate Dehydrogenase and 6-Phosphogluconic Dehydrogenase Deficiencies in Population of the United States, South Vietnam, Iran, and Ethiopia. J Lab Clin Med 81:603, 1973
18. Lampe RM, Kirdpon S, Mansuwan P, et al: G6PD Deficiency in Thai Children with Typhoid. J Peds 87:576, 1975