Glucose-6-Phosphate Dehydrogenase Deficiency in Greece

By Leda Zannos-Marolea and Christos Kattamis

Part I

Glutathione Stability and Glucose-6-Phosphate Dehydrogenase Activity in Erythrocytes of Greek Patients with Favism

Workers in Italy,1-3 Israel4-9 and America10,11 have shown that the glutathione (GSH) instability and decreased glucose-6-phosphate dehydrogenase (G-6-PD) activity, which are characteristic of primaquine sensitive individuals, are also present in persons who develop acute hemolytic anemia following ingestion of fava beans.

The above authors1-3,11,12 have presented evidence that the biochemical defect in favism has a similar hereditary pattern; it is, most probably, transmitted by a sex-linked gene of intermediate dominance.

Final proof that the erythrocyte defect present in subjects sensitive to fava beans is identical to that of subjects sensitive to primaquine was obtained by Larizza and his associates13 who gave primaquine in therapeutic doses to an individual with a past history of favism and produced a hemolytic reaction.

Favism is very common in Greece. Biochemical studies on Greek patients with favism were first reported by one of us (Z-M.L.) in a communication presented at the 7th European Congress of Hematology in London (1959).14 Until then the characteristic enzymatic defect had been studied only in Americans of Greek extraction.11 The present paper is an extension of this first communication and includes the findings already reported.

The main purpose of this study was to investigate the biochemical defect in favism during the stage of acute hemolysis. The examination of our cases during the acute stage was, to a certain extent, imposed upon us; the severity of their condition made the need for urgent treatment with blood transfusions imperative and this prevented us from studying them at any other time except that preceding treatment. On the other hand, parents would seldom cooperate and bring their children for examination two to three months after the hemolytic episode.

Another reason that stimulated us to study our patients during the early phase of the hemolytic reaction was the lack of unanimity in the reports of the literature concerning the GSH levels, GSH stability and G-6-PD activity in "sensitive" individuals during that period.6,8,12,13-19

The recent observation that the biochemical defect is much more severe in Caucasians than it is in Negroes19,20 has been a further stimulus to examine the cases of the present study during the course of acute hemolysis. According to Marks19 young erythrocytes in "sensitive" Caucasians are almost equally

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Deficient in enzyme activity as are old ones. Assay of G-6-PD activity in "sensitive" Caucasians during a hemolytic crisis should, therefore, show very little change. Assuming that there is good agreement between results of the GSH stability test and assay of G-6-PD activity in "sensitive" individuals, during a hemolytic crisis, one might also expect very little change of GSH instability in Caucasians.24

One more purpose of this investigation was to test the genetic hypothesis in favism. We have therefore also examined the blood from the parents and siblings of our cases, whenever these were available.

**Material**

The material of this study was divided into the following groups:

1. Forty children with favism admitted to the Pediatric Clinic of Athens University. Their blood was examined before the institution of any treatment, i.e., usually 2–4 days after the ingestion of fava beans and in only one instance after the seventh day.

2. The parents of the above patients, i.e., 40 mothers and 34 fathers as well as eight siblings. Four more mothers and three fathers of female patients were also included in this group. The diagnosis of favism in their children has been made on the basis of a typical history and the clinical and routine hematologic findings.

3. Forty male children chosen at random among the patients of the hospital with various non-hematologic diseases, used as controls.

4. Eight children with a past history of favism.

5. Two hundred and two children with favism admitted to the Pediatric Clinic during the years 1953–58. The diagnosis of favism had been made on the basis of the history and the usual clinical and laboratory findings. This group was used in the determination of the male:female ratio and the age distribution in Greek patients with favism together with groups 1 and 4.

Groups 1–4 were investigated by either the two or the three methods described below.

**Methods**

The method of Grunert and Phillips, as modified by Beutler,21 was used in the determination of reduced glutathione (GSH). The blood was freshly drawn or had been stored in the ice-box for 24 hours. Glucose, 400 mg. per 100 ml. blood was always added, as suggested by Szeinberg.6 GSH stability was tested as described by Beutler.21

The activity of G-6-PD was measured by a simple photometric test devised by Motulsky2 in which brilliant cresyl blue is used as an indicator of the reaction:

\[ \text{G-6-PD} + \text{TPN}^+ \rightarrow \text{6-Phosphogluconate} + \text{TPNH} + \text{H}^+ \]

catalysed by the enzyme. The dye is colorless in the reduced state and the time taken for decolorization under standard conditions is less than 100 minutes with normal G-6-PD activity.

This method was used mainly of necessity and with full appreciation of the fact that it was meant to be applied for screening purposes, i.e., for the detection of male "reactors" far from hemolytic episodes. It was thought worth trying it in our patients for the following reason: Caucasians have a more severe G-6-PD deficiency than Negroes, their young erythrocytes being almost as equally enzyme-deficient as old ones. It would be expected, therefore, that in our patients, the Motulsky test might be reliable also during a hemolytic crisis.

Except for these theoretical considerations there was also the practical aspect of a rapid and easy diagnosis that stimulated us to use the Motulsky test. Patients with favism are admitted to the clinic in great numbers during a short period of time every year and blood specimens must be drawn before treatment is instituted. Under such circumstances the diagnosis of enzyme deficiency would not be easy if it depended on the glutathione stability method.
In most cases oxalated blood was used. Motulsky recommends heparin, although he obtained good results with other anticoagulants.

We have gained a wide experience with this test and believe it works well when applied to the detection of male carriers, provided two points are taken into consideration. First, the hemoglobin content of the solution; we have always corrected the hematocrit in severely anemic cases. Second, the time between the addition of the blood and that of the reagents; if this time is above 30 minutes, many false positive results are obtained.

In our control group of 200 normal children, decolorization time never exceeded 80 minutes. Nevertheless, in this study, as suggested by Motulsky, 100 minutes was considered the upper limit of normal. The test was always repeated in cases with abnormal times of decolorization.

RESULTS

1. Reduced Glutathione and GSH Stability in Red Cells

a. Controls: Table 1 shows that in the control group, GSH values were in agreement with those reported in the literature for normal individuals. After incubation with acetylphenylhydrazine, GSH levels were never below 40 mg. per cent packed RBC, which is considered the lower limit of normal.

b. Patients with favism: Since data on GSH and GSH stability before ingestion of fava beans were lacking in the patients of the present study, the findings obtained during the hemolytic crisis were compared to those of the "sensitive" group. This comprised fathers of female patients and children with a past history of favism (table 1).

Results are illustrated in table 1 and figure 1 and, more analytically, in table 2. Table 1 demonstrates that the mean pre-incubation GSH was significantly lower than the corresponding mean of the "sensitive" group. When each patient was considered separately, a great variability was observed in the pre-incubation GSH, which was very low in a few cases (Cases 1, 10, 14, 16, 31, 35, 39) i.e., less than the lowest GSH encountered in the "sensitive" group. (24 mg. per cent packed RBC). This seems to indicate that, at least in some of

Table 1.—Glutathione (GSH) Levels Before and After Incubation with Acetylphenylhydrazine (APH) in the Erythrocytes of Controls, Patients with Favisim and Their Parents and Children with a Past History of Favism

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of cases</th>
<th>GSH before incubation with APH, mg.% packed RBC</th>
<th>GSH after incubation with APH, mg.% packed RBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Controls</td>
<td>40</td>
<td>Mean: 66.5, Standard deviation: 11.0, Range: 50-100</td>
<td>Mean: 53.9, Standard deviation: 9.6, Range: 40-85</td>
</tr>
<tr>
<td>3. Mothers</td>
<td>44</td>
<td>Mean: 54.0, Standard deviation: 20.6, Range: 18-110</td>
<td>Mean: 34.9, Standard deviation: 14.5, Range: 11-73</td>
</tr>
<tr>
<td>5. Fathers of female patients</td>
<td>7</td>
<td>Mean: 34.0, Standard deviation: 12.4, Range: 24-56</td>
<td>Mean: 7.0, Standard deviation: 3.0, Range: 3-13</td>
</tr>
<tr>
<td>7. &quot;Sensitives&quot; (Groups 5,6)</td>
<td>17</td>
<td>Mean: 45.0, Standard deviation: 22.0, Range: 24-103</td>
<td>Mean: 8.5, Standard deviation: 4.1, Range: 3-17</td>
</tr>
</tbody>
</table>
the patients, there was a drop of pre-incubation GSH during acute hemolysis.

Correlation of the patients' pre-incubation GSH to the time which had elapsed between the ingestion of fava beans and the examination of blood showed high levels of GSH when the interval was four days or more (with the exception of Case 40). This would agree with Flanagan's findings that GSH rises as hemolysis progresses. Yet, there were equally high GSH values with intervals of two and three days.

As illustrated in table 1 and 2 the mean post-incubation GSH was significantly higher than the corresponding mean of the "sensitive" group. Results indicate, therefore, a decrease of GSH instability during acute hemolysis. However, when studied individually, a great number of patients showed very low values of post-incubation GSH (below 10 mg. per cent packed RBC: Cases 1, 8, 12, 13, 15, 16, 19, 31–36). The possible meaning of this finding will be discussed later.

No correlation could be found between the degree of anemia or reticulocytosis and GSH instability.

In all but one patient (Case 18), post-incubation GSH was always abnormal, i.e., below 40 mg. per cent packed RBC. It follows that the diagnosis of the biochemical defect during acute hemolysis is, as a rule, possible in Greek individuals with favism.

c. Mothers of patients: Findings in 44 mothers are illustrated in table 1 and figure 1. It can be seen that the pre-incubation GSH was on the average only slightly lower than that of controls. The mean GSH value obtained after incubation was definitely abnormal, falling in the intermediate range. When studied individually, however, only 77.7 per cent of mothers could be classified as abnormal. In the remaining, post-incubation GSH did not fall below 40
mg, per cent packed RBC. In 11.1 per cent of the mothers, post-incubation GSH fell into the range of “sensitive” individuals, i.e., below 22 mg. per cent packed RBC.

d. Fathers of patients: As expected, GSH and GSH stability were normal in all fathers of male patients. On the other hand, all fathers of female patients had low GSH levels and unstable GSH, the post-incubation GSH falling below 22 mg. per cent packed RBC (table 1). Five of these fathers reported hemoglobinuria in the past following the ingestion of fava beans. The remaining two had eaten fava beans repeatedly without untoward effects.

e. Children with a past history of favism: Findings in this group are comparable to those of fathers of female patients. These two groups essentially form one category and were, therefore, put together (Group 7, table 1).

f. Two males of the eight siblings were found to be “sensitive”. Both re-
ported a past history of favism. Their findings were included in the “sensitive” group of table I.

2. Glucose-6-Phosphate Dehydrogenase Activity in Red Cells

a. Patients with favism. The time of decolorization was above 100 minutes in 25 or 83 per cent of the 30 patients examined. In the remaining five, it was above 80 minutes, which is suggestive of G-6-PD deficiency. The glutathione stability was also abnormal in these patients, with the exception of Case 21.

The Motulsky test is, therefore, of considerable value in the diagnosis of the biochemical defect during the acute stage of hemolysis; it is however inferior to the glutathione stability method.

The Motulsky test is less sensitive when it comes to the mothers of the patients. Of the 31 mothers examined, only 13 had abnormal decolorization times. Post-incubation GSH levels were below 40 mg. per cent RBC in these mothers. But there were 13 more mothers with abnormal glutathione stability who were found to be normal with the Motulsky test.

3. Fathers and Siblings of the Patients

All fathers and siblings defined as “sensitives” by the GSH stability method had abnormal decolorization times.

Male: Female Ratio and Age Distribution of Greek Patients with Favism

Figure 2 illustrates the age and sex distribution of 250 cases of favism admitted to the Pediatric Clinic of Athens University during the years 1953–60. Favism in Greece appears to be most frequent at the age of 3–6 years. After the 6th year there is an abrupt fall in the incidence of the disease. The male:female ratio is about 10:1. The same ratio has been reported by Sansone in Italy. According to the above author the ratio is different in adulthood, favism occurring twice as frequently in women than in men. The age at which the ratio begins to change is unknown. Figure 2 shows a relative increase of females after the 9th year of age, but the number of cases with favism is so very small at this age that no conclusions can be drawn.

DISCUSSION

The great variability of pre- and post-incubation GSH values observed in our patients is consistent with the lack of unanimity between data of different workers who have used the GSH stability method under similar conditions, but in a small number of patients.

Nevertheless, in spite of the wide range of GSH values, GSH stability was sufficiently abnormal in all cases (except Case 18) to permit a diagnosis of G-6-PD deficiency.

It is unfortunate that data concerning GSH and GSH stability before or long after the hemolytic episode could not be obtained from our patients. However, post-incubation GSH levels in a considerable number of them were found to be very low (below 10 mg. per cent packed RBC in Cases 1, 8, 12, 13, 15, 16, 19, 31–36). Comparison of these values with those obtained from the “sensitive” group (Group 7, table 1) suggests that in the above cases, GSH in-
stability was not decreased during the hemolytic crisis. This would be consistent with the hypothesis that in Caucasians young erythrocytes are almost equally G-6-PD deficient as old cells.

Results obtained with the GSH stability method in 44 mothers are in agreement with data of other authors who reported normal values in some female heterozygotes.

In 11.1 per cent of the mothers very low post-incubation GSH levels were observed which were comparable to those found in female homozygotes or "sensitive" males. This has also been described by other workers. These mothers had eaten fava beans repeatedly without untoward effects. It is unfortunate that more extensive family studies could not be performed in these cases.

No inconsistency has been observed between the data reported in this paper and the genetic hypothesis of a sex-linked gene with intermediate dominance. It is true that the transmission of the biochemical defect through the mother in male patients was not proven in all cases, but, as already mentioned, this was to be expected. More important was the observation that all the fathers of female patients were "sensitive" and that there was a great preponderance of males among our children with favism.

Fig. 2.—The age and sex distribution in 250 patients with favism admitted to the Pediatric Clinic of Athens University during the years 1953–1960. Boys are represented by the white bar; girls by the black bar.
SUMMARY

The glutathione stability of red cells was estimated in 40 patients during acute hemolysis induced by fava beans. There were wide individual differences but in all cases except one (Case 18) the post-incubation GSH fell to levels below 40 mg per cent packed RBC which is the lower normal limit.

The GSH stability on 44 mothers and 37 fathers gave results consistent with the genetic hypothesis that in male patients the mother is the carrier of the biochemical defect, while in female patients both parents are carriers, since, as a rule, only female homozygotes suffer from hemolytic episodes. However, in only 77.7 per cent of the mothers could the biochemical defect be proved by this method.

The Motulsky test was performed in 30 of the 40 patients. It gave abnormal decolorization times in 25 or 83 per cent of the cases. This test is therefore valuable for diagnosing "sensitivity" during a hemolytic episode; it is, nevertheless, less sensitive than the GSH stability method.

The Motulsky test was also performed on 31 mothers, 18 fathers and 8 siblings. It proved to be unreliable in the detection of female heterozygotes.

PART II

GEOGRAPHICAL DISTRIBUTION AND FREQUENCY OF THE ERYTHROCYTE DEFECT: PRELIMINARY DATA

Studies on the frequency of G-6-PD deficiency in Greek subjects have been reported so far only in Americans of Greek extraction. Interestingly enough, among the Greeks examined, it is only in individuals originating from the island of Rhodes that the erythrocyte defect was found to be present. This is
in agreement with the prevailing opinion among physicians in Greece, that favism, although widely distributed, is however much more frequent in certain parts of the country.

It is to test this hypothesis, i.e., the uneven distribution of G-6-PD deficiency in Greece, that we have undertaken field studies in different areas, using the Motulsky screening method.

In this paper preliminary data of the investigation will be presented, as well as a mapping of the geographical distribution of the enzyme deficiency among 76 parents of patients with favism admitted to the Pediatric Clinic of Athens University.

The investigation was started in areas known to physicians for years as having a high incidence of favism. Among these the islands of Cyprus and Crete were considered to be the most representative and were therefore preferred.

On the other hand three groups of individuals were chosen for comparison, which were more or less representative of the country as a whole. These were: (1) medical students of Athens University; (2) newborns of a maternity hospital in Athens and (3) patients treated at the Pediatric Clinic of Athens University.

The choice of islands as the first areas to be investigated was influenced by statistical data on malaria morbidity rates in Greece during the years 1905–1936 (previous data do not exist). According to these data, the islands had a much lower morbidity rate as compared to the mainland. If the hypothesis advanced by Motulsky that malaria is a selective agent for the maintenance of G-6-PD deficiency in human populations is correct, then the frequency of the erythrocyte defect should probably be lower in the islands than in other parts of Greece with a high malaria morbidity. The latter areas will be investigated subsequently. As the same theory has been formulated for the sickle-cell trait, areas with a high incidence of sickling will also be studied. Interestingly enough, sickle-cell anemia is rare in the islands and practically non-existent in Cyprus and Crete.26

To summarize, the aim of the present investigation, preliminary data of which are reported in this paper, was to study four large groups of Greek individuals:

Group A: Individuals representative of Greece as a whole.
Group B: Individuals originating from areas with a high incidence of favism and a relatively low malaria morbidity.
Group C: Individuals originating from areas with a high incidence of favism and a high malaria morbidity.
Group D: Individuals originating from areas with a high incidence of favism, a high incidence of sickling and a high malaria morbidity.

If the above mentioned two hypotheses be correct, it would be expected that G-6-PD deficiency has a different frequency in each of the above groups, being lowest in group A and highest in groups C and D.

MATERIALS AND METHODS

The material of this investigation consisted of the following groups:
G-6-PD DEFICIENCY IN GREECE

1. Three hundred and ten male adults treated at the General Hospital of Nicosia, Cyprus, for various non-hematologic diseases.
2. Three hundred and ten male healthy adults and school children from Herakleion, Crete, and the neighboring villages.
3. Three hundred full-term male newborns delivered at the Maternity Hospital Marica Heliadi, Donation Helena Venizelos, Athens.
4. One hundred and thirty male medical students at Athens University.
5. One hundred and fifty male children treated at the Pediatric Clinic of Athens University for various non-hematologic diseases.
6. Seventy-six parents of children with favism who were used for the mapping of the G-6-PD deficiency in Greece. They consisted of 71 mothers and 5 fathers of female patients. The enzyme abnormality was proven by the glutathione stability method in only 40 of the children (Group 1 in Part I of this paper). In the remaining, the diagnosis of favism had been made on the basis of the history and the usual clinical and laboratory findings.

Motulsky’s screening test was applied in all cases. It was considered positive for G-6-PD deficiency when the blood failed to decolorize before 120 minutes. Considering that the blood of “sensitive” males who are not in a hemolytic crisis decolorizes as a rule between 2-24 hours, we have not included among the “positives” the individuals with decolorization times between 100-120 minutes.

The blood was drawn from the finger and no anticoagulant was used except in the Cyprus cases (oxalate). Only males were examined, because this test is not very reliable in the detection of “intermediates.”

RESULTS

Cyprus: Abnormal times of decolorization were found in 10 or 3.2 per cent of the 310 Cypriots. There were two individuals with decolorization times of 110 minutes who have not been included among the “positives”.

Crete: All of the individuals examined originated from villages of the prefecture of Herakleion with a known high incidence of favism.

Of the 310 blood specimens taken in Crete, 104 had to be rejected because of hemolysis, due to the fact that they were put by mistake into the deep freeze. It is significant, however, that 3 of these 104 individuals were reported to have had hemoglobinuria after ingestion of fava beans.

Of the remaining 206 individuals, 6 or 2.9 per cent were found to be G-6-PD-deficient.

Newborns: The blood was drawn between 2-7 days of life and the choice of the newborns was made at random, irrespective of the degree of jaundice present.

Of the 300 newborns, 3 were found to have G-6-PD deficiency. One of them was so deeply jaundiced on the 5th day of life, that he required an exchange transfusion. There was no blood group incompatibility in this baby and the jaundice was attributed to the enzymatic abnormality in spite of the fact that none of the known toxic drugs had been administered. The other babies appeared quite normal. In one of them, glutathione stability was determined on

*Hemoglobin determinations were not done as they are not necessary when the Motulsky test is employed in field studies. In rare cases with severe anemia, the color of the hemolyzed blood is so light that the latter can be easily diagnosed. One can then just add more blood, until one gets a good color. The test works very well with a wide range of hemoglobin concentrations.
the 4th day of life, after addition of glucose to the blood and was found to be abnormal. (Pre-incubation GSH: 53 mg. per cent packed RBC; post-incubation GSH: 4 mg. per cent packed RBC.) The frequency of G-6-PD deficiency was, therefore, 1 per cent.

Only 6 per cent of the newborns originated from Athens (origin of mothers); the remaining came from Peloponnesos, the islands and the mainland. There were no cases from the north of Greece.

Students: All the students examined had a normal Motulsky test. Only 3 per cent of them originated from Athens, the remaining were more or less representative of the whole country, with the exception of northern Greece.

Children: There was only one G-6-PD-deficient case among 150 children examined. The frequency of the enzymatic abnormality is therefore 0.7 per cent.

Geographical Distribution of Favism

Figure 3 represents a map of Greece. The numbers on the map correspond to carriers of the biochemical defect (71 mothers and 5 fathers of female patients) and show a wide distribution of G-6-PD deficiency. They do not indicate, however, the frequency of the erythrocyte abnormality because the reasons why the patients with favism are transferred to the Pediatric Clinic for treatment depend on factors that are not easy to determine. Among them, most important, are the possibility of local treatment with blood transfusions, the distance from Athens, the economic status and the degree of civilization of the patients' families.

Fig. 3.—Map of Greece, showing the geographical distribution of G-6-PD deficiency (71 mothers and 5 fathers of female patients).
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Discussion

Results on G-6-PD deficiency in Cyprus and Crete show a frequency of approximately 3 per cent. It is most probable, however, that a more detailed study, especially in Cyprus, would have shown an uneven distribution of the defect within the island and therefore a higher incidence in certain areas.

The data obtained in Athens from the three groups selected for comparison show a significantly lower incidence of 0.7 per cent. Among them, the newborn group had the highest incidence. This was expected for the following reasons:

A certain number of G-6-PD deficient Greek newborns suffer from severe neonatal jaundice,\textsuperscript{27} although none of the known toxic drugs is administered to them. Similar cases have been described recently in the yellow race.\textsuperscript{28,29} This often leads to kernicterus if treatment with exchange transfusions is not promptly instituted. But exchange transfusions can be adequately performed only in a few big towns of Greece. Considering the difficulties of treatment and the ignorance of most peasants of the dangers of severe jaundice, it is to be expected that a certain percentage of G-6-PD deficient newborns will either die from kernicterus or survive with severe neurologic sequelae. These “lost carriers” should be taken into consideration in any study of the frequency of G-6-PD deficiency in Greece, particularly when children attending regular school or University students are chosen for investigation. As their frequency is unknown, comparative studies should be preferably made on newborn groups, but this is not very easy for practical reasons.

Summary

G-6-PD deficiency is widely disseminated in Greece; it is, however, not evenly distributed throughout the country.

The highest frequency of G-6-PD deficiency found so far in males was about 3 per cent; the lowest was 0.7 per cent.

Summary in Interlingua

Deficientia de dishydrogenase de glucosa-6-phosphato es extensemente disseminate in Grecia. Tamen, le condition non es distribuite uniformemente in omne le partes de ille pais.

Le plus alte incidentia del deficientia de dishydrogenase de glucosa-6-phosphato incontrate usque nunc in un population mascule eseva circa 3 pro cento, le plus basse 0.7 pro cento.

Acknowledgments

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