J. med. Genet. (1969). 6, 34.

Favism

Clinical and Biochemical Data

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In Greece, favism is the most common type of acute haemolytic anaemia in childhood (Kattamis, unpublished). The disease seems to be restricted mainly to certain Mediterranean countries (Sardinia, Greece, and Israel, especially among Sephardic Jews); lately, it has also been described in other areas of the world (Motulsky and Stamatoyannopoulos, 1966).

Many aspects of the pathogenesis of favism have been elucidated in the past decade through the evolutionary progress in the study of G6PD deficiency (Beutler, 1965; Motulsky, 1965), and it was shown that favism affected only individuals with G6PD deficiency (Szeinberg *et al.*, 1957; Sansone, Piga, and Segni, 1958; Zannos-Mariolea and Kattamis, 1961). This red cell enzymatic defect is inherited as a sex-linked character; it exists in a number of variants, and is also related to the haemolytic syndrome which follows primaquine and other drug administration (Tarlov *et al.*, 1962), severe neonatal jaundice unrelated to rhesus or ABO incompatibility (Fessas, Doxiadis, and Valaes, 1962), congenital type I non-spherocytic haemolytic anaemia and haemolytic anaemia due to infection (Choremis *et al.*, 1966; Kattamis and Kyriazakou, 1966). Until now favism has been described only in individuals with the common Mediterranean type of G6PD deficiency, which is widely, though unevenly, distributed in Greece (Choremis, Zannos-Mariolea, and Kattamis, 1962; Choremis *et al.*, 1963a, Allison *et al.*, 1963; Stamatoyannopoulos, Panayotopoulos, and Motulsky, 1966b).

The pathogenesis of favism, though directly related to the Mediterranean type of deficiency, is still obscure. Accumulating data suggest that additional factors, probably genetic, are required for the development of this peculiar haemolytic syndrome (Stamatoyannopoulos *et al.*, 1966a; Kattamis and Chaidas, unpublished).

The variation of the clinical picture in the patients with favism and the relation of the clinical symptoms to enzymic disturbances have not been thoroughly investigated yet.

In this communication, data on some clinical and biochemical aspects of favism in 506 patients are presented, in an attempt to elucidate some features of the disease that are still largely unknown or unexplained.

Material and Methods

The material includes 506 patients admitted to our hospital between the years 1955 and 1966. Data before 1962 were collected in retrospect from the hospital records. The 120 patients seen after 1962 were studied in detail.

The material was restricted to the 0–15 year age-group. Attempts to identify a large number of cases of favism among adults were unsuccessful. Even in active general hospitals only isolated cases of favism were found. These patients were excluded from the present study in order to ensure a homogeneous group.

Favism was diagnosed only in the presence of clinical and/or laboratory findings of acute haemolytic syndrome after ingestion of fava beans. Clinical signs were haemoglobinuria, anaemia, and mild jaundice. In the absence of gross clinical manifestations the diagnosis was based on haematological findings compatible with the presence of acute haemolysis. In this respect the presence of characteristic morphological changes of erythrocytes in peripheral blood smears proved helpful; these changes consisted of fragmented cells, spherocytes, and rarely burred cells (Fig. 1).

Haemoglobin, haematocrit, reticulocytes, and bilirubin were studied by routine methods. G6PD activity was estimated quantitatively in 64 boys and 12 girls during the acute favic crisis. Enzyme levels were reinvestigated in 20 boys during remission, in addition to 21 other boys with a past history of favism. G6PD activity was determined by the method of Zinkham, Lenhard, and Childs (1958), slightly modified. The method has been described in detail elsewhere (Kattamis,

Received June 24, 1968.

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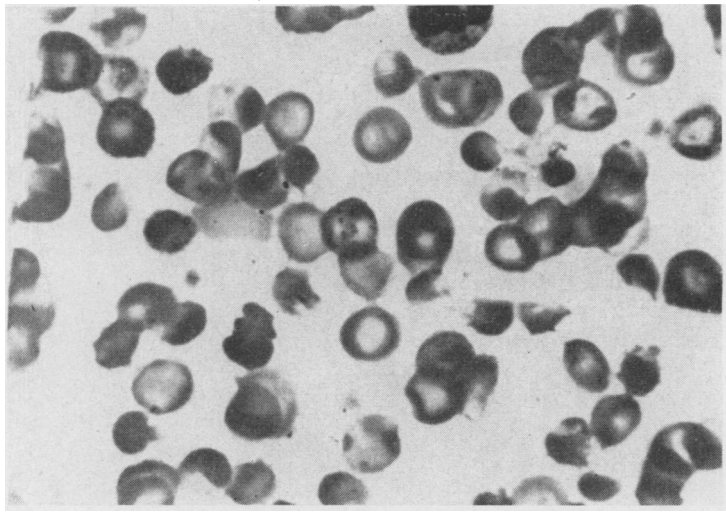

FIG. 1. Morphological changes in erythrocytes occurring during favism.

1963). Our standards for 130 normal children were 396 ± 61, U./100 ml. packed red cells, with a range of 296–610 U. per 100 ml. packed red cells. Brilliant cresyl blue (BCB) decolorization test (Motulsky and Campbell-Kraut, 1961) was used, both for screening purposes and for evaluation of its effectiveness in detecting males deficient during crisis. Samples failing to decolorize in 80 minutes were considered suspicious; those decolorizing in more than 100 minutes were taken as evidence of deficiency. These criteria are slightly different from those used in some of our previous studies (Choremis *et al.*, 1963b).

Results

Clinical Data

Age and Sex Distribution. This is illustrated in Fig. 2. The disease was more frequent in children aged 2–5 years; 65% of the cases belonged to this group. After the age of 6 years the incidence showed a steady decline which was steeper after the age of 10 years. Only 36 patients (7·2%) were 10–15 years old. 28 patients (5·5%) were less than 12 months of age, the youngest being 45 days

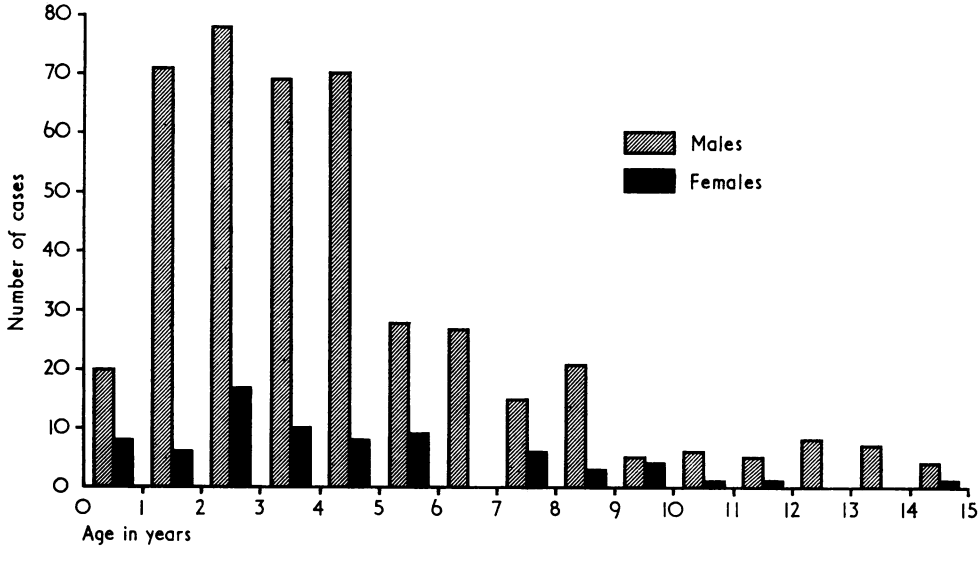

FIG. 2. Age and sex distribution in favism.

old. 18 of the 28 infants were breast-fed and here the haemolytic syndrome appeared 2–6 days after the ingestion of fava beans by the mother who was free of symptoms. The sex ratio was 6·2 male:1 female (436:70).

Seasonal Distribution. This is presented graphically in Fig. 3. The disease occurred throughout the year, though its incidence was considerably higher during the spring, especially in May, when 42% of the cases appeared. This seasonal predilection coincides with the ripening of the beans.

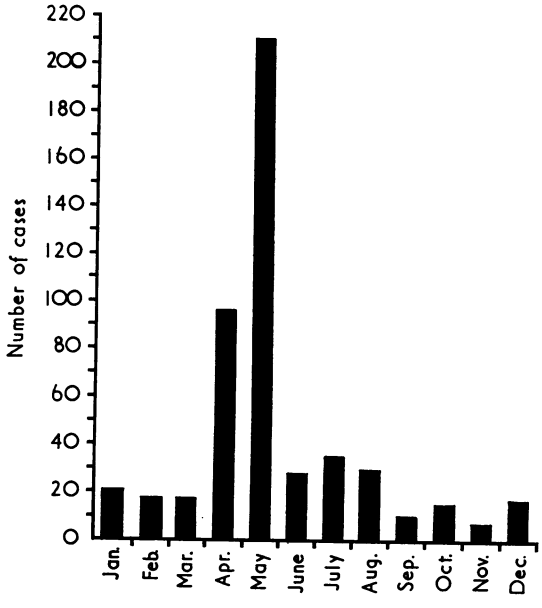

FIG. 3. Seasonal distribution in 506 patients with favism.

Detailed inquiries (Fig. 4) disclosed that 82 of 120 patients (68%) had their haemolytic episode with fresh beans, 36 (31%) with dry beans, and 2 patients had ingested both fresh and dry beans.

Onset of Clinical Symptoms. The onset of the main clinical symptoms varied from 24 hours to 9 days after eating the beans. Patients were usually admitted to hospital because of gross haemoglobinuria, severe anaemia, and mild jaundice. Fig. 4 illustrates the time between the ingestion of beans and admission to hospital. It also shows the haemoglobin levels of 120 patients on admission.

The majority of patients entered the hospital as soon as the main clinical symptoms were evident. However, some patients were admitted very early

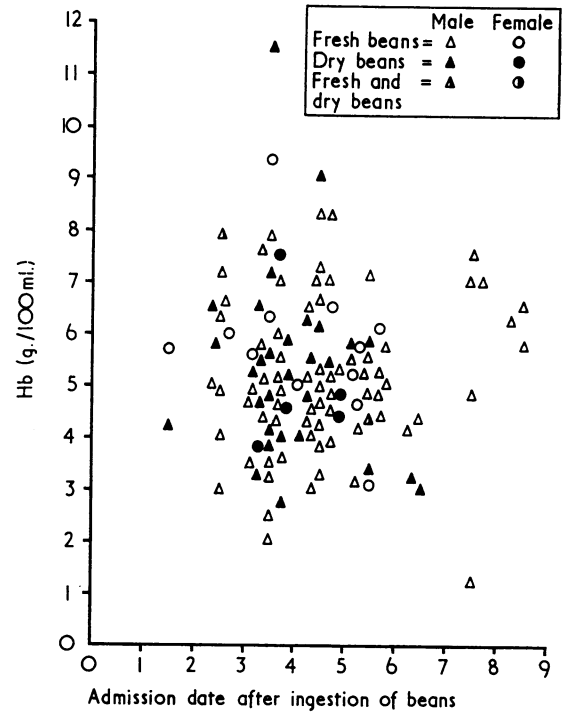

FIG. 4. Admission date and haemoglobin levels in relation to the time of ingestion of fava beans.

with high haemoglobin levels, while others were not admitted until after they had become severely ill. Fig. 4, therefore, represents only a rough indirect index of the onset of clinical symptoms. About 80% of the patients were admitted between the third and the sixth day after ingesting the beans. Only 8 patients were admitted after the seventh day. These patients were not severely affected; in only 2, was transfusion considered necessary. But all patients admitted before the sixth day were transfused, even those whose haemoglobin level was high on admission, for it soon dropped to less than 6–7 g./100 ml.

The type of beans (fresh or dry) had no influence on the onset of clinical symptoms and anaemia (Fig. 4); and no difference in the severity of the haemolytic syndrome was noted between boys and girls in this group.

Laboratory Data

Haemoglobin Levels. Fig. 5 illustrates the severity of the haemolytic syndrome more clearly. The haemoglobin levels recorded had been estimated before transfusion, when they had usually

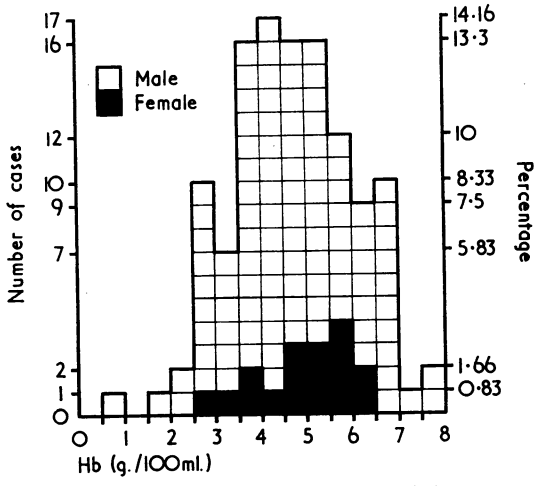

FIG. 5. Haemoglobin levels before transfusion.

dropped to 6 to 7 g./100 ml. and haemoglobinuria persisted.

Only 6 patients were not transfused. In 81% of the cases the haemoglobin was below 6 g./100 ml. before transfusion and in 30% it was less than 4 g./100 ml. on admission. In some of these cases anaemia was extremely severe, with haemoglobin ranging between 1·8 and 3 g./100 ml. All patients recovered after adequate blood transfusion.

G6PD Activity. The results of quantitative G6PD estimations in 64 male patients during crisis, and in 41 males during a period of rest are illustrated in Fig. 6; the Table shows the results in 12 female patients.

During the period of rest the enzymic activity was completely absent in 28 males (70%); the remaining patients had a low activity not exceeding 10% of the normal mean. One had an activity of 25% of the normal mean (110 U./100 ml. PRC); these levels correspond to those of the mild G6PD deficiency variant recently described in Greece (Stamatoyannopoulos, Panayotopoulos, and Papayannopoulou, 1964). All male patients studied during crisis were deficient, with G6PD activity well below the normal range. G6PD deficiency was easily detectable in male patients even by the semiquantitative BCB decolorization test. By this test we were able to detect G6PD deficiency in 49 out of the 50 male patients (98%) examined. It is evident that under optimal conditions the results of the BCB test in deficient males generally correlated well with the results of the quantitative determination of G6PD.

Of the 64 male patients studied during crisis, 14 (22%) were totally deficient. In most of the others the activity ranged between 20 and 140 U./100 ml. PRC, i.e. from 5–35% of the normal mean. Female patients showed a wider variation in G6PD activity,

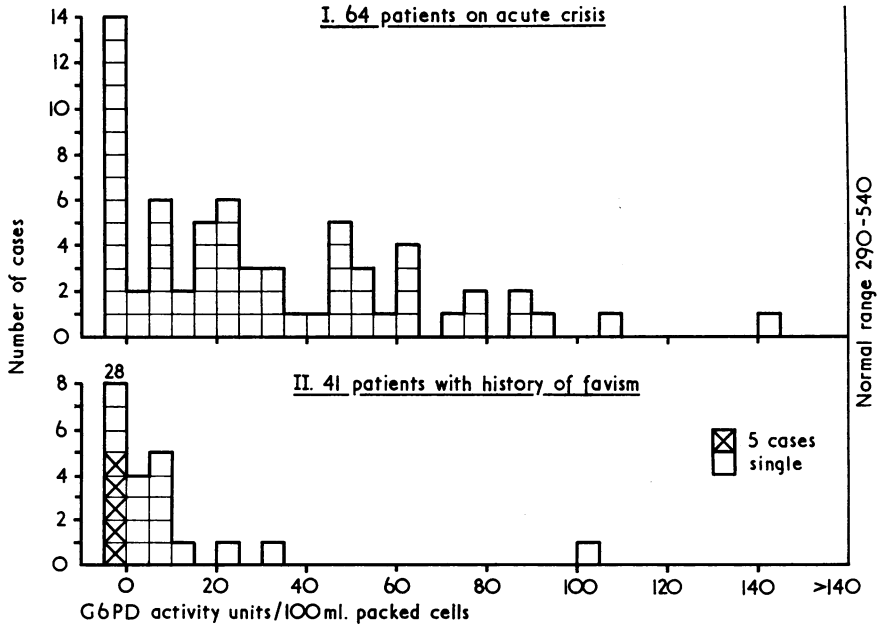

FIG. 6. G6PD activity levels in male patients with favism.

TABLE

G6PD ACTIVITY IN 12 FEMALE PATIENTS AND PRESUMED GENOTYPE BASED ON FAMILY STUDIES

Case No.	G6PD Activity (U./100 ml. PRC)	% of Normal Mean	Parents' Genotype Based on G6PD Levels		Patient's Presumed Genotype
			Father	Mother	
1	0	0	Hemizygote	Heterozygote	Homozygote (Pr)
2	28	7·2	Hemizygote	Homozygote (Pr)	Homozygote (Pr)
3	30	7·5	Hemizygote	Heterozygote	Homozygote (Pr)
4	137	34·2	Hemizygote	Heterozygote	Homozygote (Pr)
5	140	35·0	Not tested	Normal	Heterozygote (Pr)
6	150	37·5	Hemizygote	Heterozygote	Homozygote (Pr)
7	180	45·0	Not tested	Not tested	?
8	190	47·5	Hemizygote	Normal	Heterozygote
9	215	54·5	Not tested	Not tested	?
10	230	57·5	Normal	Normal (heter. Pr)	Heterozygote (Pr)
11	303	75·0	Normal	Heterozygote	Heterozygote (Pr)
12	360	90·0	Hemizygote	Normal	Heterozygote

Pr = Probable ? = not known.

i.e. from 0 to 360 units. This may be explained by the fact that affected females were either homozygotes or heterozygotes.

Pedigree studies in 10 of these females showed that 5 were probably homozygotes (Table). Unfortunately we were not able to re-examine these patients during period of rest.

Reticulocytes and G6PD Activity. During the crisis reticulocytes were always increased, indicating that the variation in G6PD levels in patients during crisis might have been associated with the degree of reticulocytosis. The relation between G6PD activity and the degree of reticulocytosis in 45 male patients is illustrated in Fig. 7, which indicates that the increase in G6PD activity was not always related to the degree of reticulocytosis; thus patients with low reticulocytes (10–15%) had high G6PD levels (80–110 U.), while others with high reticulocytes (15–25%) had low G6PD levels (0–40 U.). The absence of correlation was more evident in 9 completely deficient patients in whom the reticulocytes ranged from 6 to 25%.

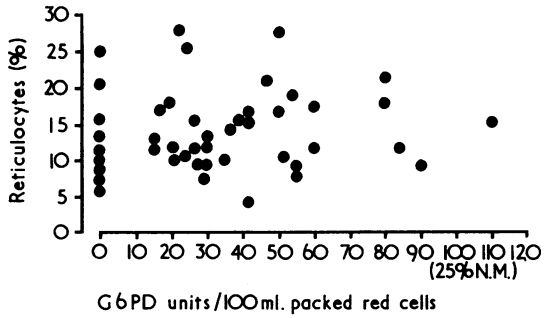

FIG. 7. Correlation of reticulocytosis to G6PD levels in patients with favism.

Discussion

Favism is primarily a disease of childhood. The predilection for very young children aged 2 to 5 years is difficult to explain. It could be argued that the incidence of favism falls as the children get older simply because affected children avoid consuming fava beans after a haemolytic episode. If this were true all patients should have a haemolytic crisis on the first and all subsequent contacts with fava beans. Careful inquiries of 120 patients disclosed that only 25% experienced haemolytic crisis after the first ingestion of fava beans, and that most of them ingested beans at a later date, with no untoward effect. The remaining 75% had had their crisis unexpectedly, though they had ingested fava beans several times. Among these patients additional differences in susceptibility to fava beans were detected. In 10 children a second attack was reported, in 4 a third, and in 1 several attacks. Most of the deficient members of the latter's family, including females, were highly sensitive to fava beans (Kattamis, unpublished).

Fava beans do not necessarily produce haemolytic crisis in all G6PD deficient individuals. In Greece the incidence of favism in 223 deficient males was 10·3% (Kattamis, 1967b). Siniscalco *et al.* (1961) reported a higher incidence of favism (about 20%) among 121 deficient individuals in Sardinia. Thus, favism differs considerably from the haemolytic syndrome caused by drugs in Negroes deficient in G6PD. All sensitive subjects are known to develop a self-limited haemolytic syndrome after the administration of an adequate dose of primaquine (Tarlov *et al.*, 1962; Beutler, 1965). For favism, we are still ignorant of the nature of the noxious agent as well as of the dose that is capable of producing haemolysis. It may be assumed that the higher susceptibility of younger children, as well as

of the small percentage of G6PD deficient individuals who are sensitive to fava beans, may be associated with differences in the absorption or the metabolism of the noxious agent, resulting in an increase of its concentration in the blood.

Similarly, the high incidence of favism in May may be related to differences in the nature or the concentration of the noxious agent in fresh fava beans. Similar differences may also exist in fresh beans at different stages of ripening.

Unlike Sansone *et al.* (1958), we found no case of favism after inhalation of pollen from the fava plant. The low incidence of the disease in March, when plants are in blossom, is additional indirect evidence that inhaled pollen does not commonly precipitate favism in this country.

The preponderance of males in this series is easily explained by the sex-linked character of the enzymic defect in G6PD deficiency, which is fully expressed in males. Nevertheless, unpublished observations on mothers of males affected by favism, who had ingested fava beans at the same time as their children, suggest that a considerable percentage of these mothers develop a mild compensated haemolytic syndrome which escapes diagnosis. Thus, the 6.2:1 male:female ratio is apparently not the real one, but only that of the selected, severe, hospitalized cases (Kattamis and Chaidas, unpublished).

Mild clinical illness after the consumption of fava beans has been previously noted by Italian authors, but until now its incidence and laboratory features have not been fully defined.

In the present series the haemolytic process was rapid; in 81% of the patients the haemoglobin dropping to very low levels usually two to four days after the ingestion of fava beans. It is of interest that in 6 out of 8 patients with a low rate of haemolytic process, haemoglobin was kept above 6 g./100 ml., haemoglobinuria was not apparent, and the whole syndrome was self-limiting.

Jaundice was as a rule very mild, except in two cases where bilirubin levels exceeded 15 mg./100 ml.

All patients except one, examined during a period of rest, showed a total or nearly total absence of enzymic activity, ranging from 0–10% of the normal mean. Considering the affinity of the abnormal enzyme to reduce triphosphopyridine nucleotide, the above results indicate that patients with favism carried the severe Mediterranean type of G6PD deficiency. Only one patient examined during rest seemed to have the mild type of G6PD deficiency: to our knowledge this is the first person with the mild type of deficiency who is reported to have haemolysis after ingesting fava beans. Therefore, detailed studies are necessary to establish the sensitivity to fava beans of the different types of G6PD deficiency in Greece.

In most male patients some increase in enzyme activity was found during crisis, but it never exceeded 10–35% of the normal mean.

Female patients were few, but their haemolytic syndrome was similar in severity to that of males. During crisis the enzyme levels showed a wide variation which may be explained by the fact that female patients were either homozygotes or heterozygotes. Logically, favism may affect any female heterozygote; the severity of the haemolytic syndrome would vary greatly, depending on the percentage of deficient erythrocytes. The percentage of deficient cells and G6PD activity in female heterozygotes varies from complete absence to normal; most heterozygotes have intermediate levels of activity (with a shift to the normal) (Davidson, Childs, and Siniscalco, 1964), and two populations of erythrocytes—one normal and the other deficient (Kattamis, 1967a). In each individual, G6PD levels are determined mainly by the percentage of normal cells, which is constant in each heterozygote, depending on the percentage of cells in which the deficient X chromosome was inactivated during the period of Lyonization. A severe haemolytic syndrome may be expected only in homozygotes or heterozygotes with a low enzymic activity and a high percentage of deficient erythrocytes. Our findings in G6PD activity on female patients are compatible with this hypothesis.

In female homozygotes the increase in G6PD activity is supposed to be similar to that of male hemizygotes; in heterozygotes it varies greatly, depending not only on the proportion of deficient young erythrocytes but mainly on the proportion of normal (old and young) erythrocytes which are not haemolysed. The normal G6PD activity found in 2 of the severely anaemic female patients is not surprising; it could be explained even in the presence of only a small percentage of normal cells, since during crisis, when all the old deficient cells are destroyed, the measurable activity depends on young deficient erythrocytes, on all normal unhaemolysed old cells, and on an increased number of normal young erythrocytes with a very high activity. Considering the G6PD activity and reticulocytosis observed during acute crisis it would be possible in certain instances to distinguish between a heterozygote and a homozygote female. Most female heterozygotes are expected to have enzymic activity above the level found in male hemizygotes during crisis, i.e. more than 35% of normal mean.

The increase in enzyme activity during crisis

seems to be related to the destruction of old cells and the overproduction of young erythrocytes. In fact, at the height of the haemolytic process a homogeneous red cell population with young erythrocytes is formed. As previously established, the young red cell population in the Mediterranean type of G6PD deficiency has an activity of about 30% of normal mean, compared to that of <1% of the old population.

These values correlate well with G6PD activity found in most of our male patients during crisis; the increase in enzyme activity should be related most probably to the percentage of young erythrocytes. However, the degree of reticulocytosis in 45 male patients showed no direct relation to G6PD activity levels (Fig. 7). This was more clearly demonstrated in 9 patients with a complete absence of enzymic activity in whom the reticulocytes ranged from 6–25%. All these patients also had haemoglobin levels below 6 g./100 ml., suggesting that most red cells were young.

These findings indicate that in Greeks with the severe Mediterranean type of deficiency, G6PD activity in young erythrocytes varied greatly, and might be completely absent in some cases. This observation stands as further indirect evidence that, in Greece, the severe Mediterranean type of deficiency is heterogeneous (Kirkman *et al.*, 1965).

The variation of enzymic activity in young deficient erythrocytes also suggests that differences in the clinical signs in favism may be associated with the degree of deficiency of young erythrocytes. It is reasonable to assume that patients with grossly deficient reticulocytes are those who are prone to severe or even fulminating haemolytic disease, which may be fatal if untreated, for the grossly deficient reticulocytes are less resistant to haemolysis than those that are not completely deficient.

Undoubtedly, further studies are necessary to establish the heterogeneity of the Mediterranean type of deficiency in Greece, as well as the relation between enzyme variants and the pathogenesis of the clinical manifestations of favism.

Summary

Clinical aspects of favism were studied in 506 patients aged 0 to 15 years, and detailed haematological and biochemical investigations were performed in 120 of them.

Favism affects mainly children aged 2 to 5 years. The male:female ratio was 6·2:1 (436:70). It occurs throughout the year, with a peak in May, after the ingestion of either fresh or dry fava beans, but not after inhaling the plant's pollen.

The haemolytic syndrome was severe even in females. 30% of the patients were admitted with Hb below 4 g./100 ml.; levels as low as 1·8 g./100 ml. were noted. The mortality rate was reduced to zero after proper treatment. Only 5% of patients had a self-limiting attack. On remission a total or nearly total G6PD deficiency was detected in all patients but one. During the crisis, an increase in G6PD activity ranging from 10–35% of the normal mean was observed, which was attributed to the overproduction of young erythrocytes.

In a good number of cases the increase of enzymic activity was not proportional to the degree of reticulocytosis, indicating that in deficient reticulocytes G6PD activity may range from 0 to as high as 35% of the normal mean. These differences in the activity of deficient young erythrocytes favour the hypothesis that G6PD deficiency in Greece is heterogeneous, and offer an explanation for the variations observed in the severity of the haemolytic syndrome.

Ch.A.K. was in receipt of a WHO exchange research workers grant. The work was partly supported by the Royal Hellenic Research Foundation (grant 743).

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