FAVISM IN ENGLAND—TWO MORE CASES

BY

J. M. HOLT and R. A. SLADDEN

From the Nuffield Department of Clinical Medicine, The Radcliffe Infirmary, Oxford, and the Department of Pathology, Northampton General Hospital, Northampton

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Vicia faba (L), the broad bean, contains a potentially toxic substance, the exact nature of which is unknown, capable of producing a haemolytic crisis in a susceptible person. The crisis may be induced by eating the beans raw or, less commonly, cooked, and in some cases by inhalation of the bean pollen. The erythrocytes of susceptible individuals are deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD). The defect is transmitted as a sex-linked dominant trait, and shows a variable degree of penetrance (Hargreaves, 1963). Favism cannot, however, be induced in all those people who are deficient in erythrocyte G6PD, which suggests that there is a second abnormality in patients with this disease, which has yet to be defined.

Favism has been known for many centuries along the Mediterranean littoral, and it may have been one reason why Pythagoras forbade his followers to eat beans and he himself was slain rather than set foot in a bean field (Arie, 1959).

The condition was first described in Britain only 11 years ago in two Cypriots (Diggles, 1953), and since then only five other cases have been reported in this country. These included a Cypriot child (Gower and Frommer, 1960), an English child of Mediterranean ancestry (Discombe and Mestitz, 1956), an English child (McCarthy, 1955), and two English women (Brodrribb and Worssam, 1961; Davies, 1962).

In spite of the ubiquity of the broad bean and the recent increase in immigration from the Mediterranean area, this potentially lethal, yet largely preventable, condition remains little known and rarely described in this country. It may well become more common, and this report of two further cases, one of which might have proved fatal, will serve as a reminder of its existence.

Case Reports

Case 1. J.W., a 14-year-old schoolboy, had been well until early in June 1963, when he began to complain of tiredness and he was noticed to be listless and apathetic. On the evening of July 31 he was extremely tired and the following morning he fainted. Later that day he complained of noises in the ears and he vomited at frequent intervals. He became very drowsy. On the morning of August 2 he was admitted to the Radcliffe Infirmary, Oxford, desperately ill, jaundiced, weak, and barely able to respond to question or command. Examination showed a regular pulse of 132, blood pressure of 105/55 mm. Hg, and temperature of 102° F. (38.9° C.). There was a soft apical systolic murmur and the plantar responses were extensor.

The urine was dark red, and spectrophotometry confirmed the diagnosis of haemoglobinuria.

LABORATORY INVESTIGATIONS. Haemoglobin 4·3 g./100 ml. White cells, 18,100/c.mm.; reticulocytes 29%. Blood film: fragmentation of the red cells; 4 normoblasts/100 leucocytes. Heinz bodies: considerable numbers present. Serum bilirubin 7·0 mg./100 ml. Blood urea 61 mg./100 ml.

Acute haemolytic anaemia was diagnosed and, following the transfusion of whole blood, the boy's condition promptly improved.

About three weeks previously the boy had fallen into the river Thames, but there was no evidence to support a diagnosis of Weil's disease. No malarial parasites were found in thick blood films. On the other hand, the erythrocyte G6PD level (method of Prankerd, 1962) was found to be 0·4 units (normal range 2·1-4·2 units), suggesting that the haemolytic anaemia was related to G6PD deficiency.

On further inquiry, the boy's mother, who was dark skinned and claimed German nationality, admitted that she was of Greek ancestry. The boy was fair complexioned, taking after his English father. It was then found that a neighbour had given the family a large quantity of broad beans which they had been eating daily for a week. A diagnosis of favism was therefore made, and following the initial blood transfusion the boy's recovery was complete and uneventful.

The boy's mother and sister were the only members of the family who were available for investigation. Their erythrocyte G6PD levels were 2·1 and 2·6 units respectively, showing that the mother's level was at the lower limit of the normal range. Broad beans had never made
the mother feel ill, though she did not particularly like them.

Case 2. P.B., an Italian boy 10 years of age, came to this country from Southern Italy in 1961 with his parents and sister. During the evening of August 11, 1963, he complained to his parents of epigastric pain. He soon became very unwell and developed a headache.

The following morning he was seen by his doctor who found slight conjunctival icterus and was told by the parents that the boy's urine was dark. No urine was available at this time for examination. The liver edge was palpable and the boy was pyrexial. The doctor suspected infective hepatitis or, possibly, Weil's disease. He attended the boy again the following morning and sent him into Northampton Infectious Diseases Hospital the same day (August 13).

When the boy was examined in hospital he appeared sallow but not jaundiced. The following day various investigations were made.

LABORATORY INVESTIGATIONS. Haemoglobin 6·7 g./100 ml. White cells 4,500/c.mm.; reticulocytes 12%. Serum bilirubin 1·0 mg./100 ml. Liver function tests: normal. Blood film: marked polychromasia; a few normoblasts were present; no spherocytosis seen. Heinz bodies not found.

There was no history of blood loss, and the blood film suggested that a haemolytic episode had taken place. In view of the boy's nationality and the season of the year, a diagnosis of favism was suspected and the boy was transferred to the Northampton General Hospital.

No abnormal pigments, bile salts, or urobilinogen were found in the urine, but the boy later said that his urine had been 'red' at the onset of the illness. The diagnosis was confirmed by the finding of a level of 63 units of erythrocyte G6PD (method of Zinkham, 1959; normal range 150-217 units).

The father was then asked about the eating of broad beans. He said that the boy had often eaten cooked beans without ill effect, but that on the day his illness began he had eaten, for the first time, a lot of raw broad beans. When he later complained of abdominal pain, the parents were inclined to attribute this to indigestion following overindulgence. There was no knowledge of any intolerance to beans in other members of the family, but it was not possible to persuade them to attend for G6PD estimations*.

* Since this paper was written, an opportunity arose to estimate the G6PD levels in the erythrocytes of other members of the family in Case 2. The results were as follows.

Father: 2·6 units  Mother: 0·78 units
Sister: 2·5 units  P.B. (propositus): 0 units
(Method of Prankerd (1962), normal range 2·1-4·2 units.)

These figures were obtained in the course of a study which was being made by Dr. C. B. Kerr, of the Oxford Population Genetics Unit, to whom we are indebted.

The original blood sample from the propositus examined immediately after the attack of favism contained detectable amounts of G6PD. A probable explanation for this finding is that the blood then contained numerous young erythrocytes, in which small amounts of G6PD may be present, even in G6PD deficient subjects.

The boy's condition rapidly improved without any active treatment and he was sent home on the sixth day after admission, when his haemoglobin level was 9·9 g./100 ml.

Discussion

These two cases illustrate the varying degrees of severity with which favism can manifest itself. The first case might well have proved fatal, and in a large series of cases a mortality rate of 8% in children has been reported (Luisada, 1941). In the second case even the jaundice was transient, and the only real evidence of haemolysis was in the blood film.

The disease tends to be self-limiting once exposure to beans has been stopped, with selective survival of younger erythrocytes in which G6PD levels are relatively high (Beutler, 1960).

G6PD levels usually tend to be lower in affected (hemizygous) males, than in heterozygous females. In the male, the levels are dependent upon the degree of expression of the gene for G6PD deficiency. Beutler and Baluda (1964) have suggested that, in heterozygous females, coexisting populations of normal and enzyme-deficient red cells result from inactivation of the locus for G6PD deficiency in one of the two X chromosomes. The severity of the illness presumably depends not only upon the G6PD level, but also upon the amount of the bean toxin ingested or inhaled and the unknown sensitivity factor. This factor must account for the fact that while the erythrocytes of all individuals who have had favism can be shown to be G6PD deficient, not all those with G6PD deficiency develop a haemolytic anaemia when exposed to the broad bean (Hargreaves, 1963). The relatively less harmful effect on any one subject of cooked beans, as opposed to raw beans, is emphasized by the second case.

Once the condition has been diagnosed, subsequent attacks of favism are preventable in the family concerned. Individuals who are deficient in G6PD are also liable to develop a haemolytic anaemia following the administration of a wide range of drugs or from contact with some industrial chemicals. Comprehensive lists of such substances are given by Beutler (1960) and Vuopio (1963), and include 8-aminoquinoline drugs (primaquine), sulphonamides (including sulphones), vitamin K analogues, salicylates (including aspirin and para-amino salicylic acid), probenecid, and nitrofurantoin. Naphthalene, TNT, and methylene blue show increased toxicity in G6PD-deficient subjects.

Summary

Two more cases of favism in England are reported, one in an English boy whose mother was of Greek ancestry, the other in an Italian immigrant boy.
The first boy was severely affected by cooked beans; the second had previously eaten cooked beans without ill effect, but was affected by raw beans.

In both cases a deficiency of erythrocyte glucose-6-phosphate dehydrogenase was demonstrated; reference is made to the numerous chemical compounds of an oxidant nature that are capable of causing haemolysis in subjects whose erythrocytes are deficient in this enzyme.

We would like to thank Professor L. J. Witts and Dr. I. H. Gosset, under whose care these two patients were admitted to hospital in Oxford and Northampton, for permission to publish the case reports.*

In Case 1, the estimation of erythrocyte G6PD was suggested by Dr. A. A. Sharp.

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* Dr. Gosset has recently died.
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