histidinaemia, is described. No adverse effects were detected of the maternal metabolic disorder on the physical and intellectual development of the child.

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Favism in Breast-fed Infants

There is a wide spectrum of disease associated with deficiency of erythrocyte glucose-6-phosphate-dehydrogenase (G6PD). It includes favism, cases of acute haemolytic anaemia associated with the intake of some oxidant drugs, such as primaquine (Tarlov *et al.*, 1962), one variety of congenital non-spherocytic haemolytic anaemia (Wintrobe, 1967), and jaundice usually occurring during the first week of life (Shahidi and Diamond, 1959; Zinkham, 1963).

Favism is an acute haemolytic anaemia caused in a susceptible individual by eating the *Vicia fava* beans or inhaling their pollen, and is well recognized throughout the Mediterranean area, particularly in Southern Italy and Greece (Marks and Gross, 1959). A few cases have been described in the United States of America (Larkin, 1953), Great Britain (Holt and Sladden, 1965), and Germany (Gasser, 1953), as well as many countries in the Middle East. In Iraq an acute haemolytic anaemia known as Baghdad spring anaemia (Lederer, 1941) was later proved to be identical with favism, and deficiency of the enzyme G6PD was demonstrated in the affected children (Taj-Eldin, Al-Samarrae, and Al-Aboosi, 1963). In Iraq, children are the usual victims of favism, the syndrome being rare in adults (Zaki and Taj-Eldin, unpublished data). Thus, there must be factors contributing to the aetiology of this disease in addition to G6PD deficiency, inherited susceptibility, and exposure to the plant or its pollen.

During the period from 1962 until 1968 we found 4 cases of favism in exclusively breast-fed infants. Only 3 such cases have previously been reported (Emanuel and Schoenfeld, 1961; Casper and Schulman, 1956; Joannides, 1952).

Method

In Case 1 the deficiency of the enzyme G6PD was demonstrated by Motulsky's cresyl blue dye test (Motulsky and Kampbell-Kraut, 1961), and in the other 3 cases by the reduction of the tetrazolium dye spot test, as described by Fairbanks and Beutler (1962).

Case Reports

Case 1 only is described in detail; the findings in the other 3 cases are summarized in Tables I and II.

Case 1. This male infant aged 4 months, the first child of healthy Arab parents living in Baghdad, was the outcome of a normal pregnancy and labour, and had no significant previous history.

He was exclusively breast-fed. Four days before his admission in November 1962 his mother had eaten boiled, dried fava beans. Two days later he became pale and drowsy, and passed dark urine. On admission he was ill, apathetic, pale, and icteric. The heart rate was 160 per minute, respiratory rate 50 per minute, rectal temperature 37·2 °C. There were no enlarged lymph glands, the spleen was not palpable, and the liver was 2 cm below the costal margin. The mother denied taking any drugs.

Red cell count was 1,480,000/mm^3, Hb 3·8 g/100 ml, PCV 12%, reticulocyte count 7%, and white cell count 18,000/mm^3, with 55% polymorphs and no immature white cells. Total bilirubin was 4·2 mg/100 ml (indirect reacting 3·6 mg/100 ml); the direct Coombs

TABLE I

Clinical Features in 4 Exclusively Breast-fed Infants Suffering from Favism

Case No.	Age (mth)	Days Since Beans Ingested by Mothers	Duration of Pallor (dy)	Lymph Nodes	Liver (cm) Below Costal Margin	Spleen (cm) Below Costal Margin
1	4	4	2	–	2	–
2	2	5	2	–	1	–
3	4	5	3	–	–	1
4	3	4	2	–	2	–

TABLE II

Laboratory Findings in 4 Exclusively Breast-fed Male Infants Suffering from Favism

Case No.	Red cells/mm³ (millions)	Hb (g/100 ml)	PCV (%)	White blood cells/mm³ in thousands	Reticulocytes	Serum Bilirubin (mg/100 ml)		Urobilinogen in Urine
						Total	Indirect	
1	1·48	3·8	12	18	7	4·2	3·6	+
2	2·10	4·7	14	15·6	6	3·8		
3	1·90	5·2	15	22·1	12	4·5	3·2	+
4	1·21	4·0	12	19·4	10	5·0	3·5	

test was negative. Motulsky's dye test showed deficiency of G6PD.

Blood transfusion of 150 ml was given with obvious improvement. One week later the red cell count had risen to 2,100,000/mm³, and Hb to 5·5 g; recticulocyte count was 9%. The child made a complete recovery.

The other three cases were all male Arab children who were being exclusively breast-fed. In each case, the first symptom noticed was progressive pallor, occurring 2 to 3 days after the mother had eaten *Vicia fava* beans. Icterus was noticed either by the parents or on clinical examination. The urine was a deep orange colour, never red. Their previous history and family history were not contributory.

Deficiency of G6PD was demonstrated in all the cases. The mother of Case 4 showed deficiency of the enzyme, but the father's level was normal. All the cases had negative Coombs test, and normal fragility test was found in the two cases in which it was done (Cases 3 and 4). The rest of the laboratory investigations are shown in Table II; each child had a severe acute haemolytic anaemia.

Discussion

The history, clinical signs, and laboratory tests together leave little doubt that these babies had favism. They developed the disease before the flowering of the fava plant and thus could not have contracted it by inhalation of pollen. As they were all exclusively breast-fed, and all their mothers had eaten fava beans in the preceding days, the conclusion that the active agent was transferred from mother to child through breast milk is almost inescapable. The toxic agent must be able to withstand boiling and drying, and be capable of absorption from the bowel and secretion into the milk.

Summary

Four cases of favism in exclusively breast-fed infants, all males, are presented. The reactive substance in fava beans which induced the haemolysis was transmitted through mother's milk. Deficiency of the enzyme glucose-6-phosphate-dehydrogenase was proved in all the infants.

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Effects of Aspartic Acid, Orotic Acid, and Glucose on Serum Bilirubin Concentrations in Infants Born before Term

The transient unconjugated hyperbilirubinaemia of the newborn infant, most marked in those born before term, is associated with a limited ability of the liver to form bilirubin glucuronide (Vest, 1958). Bilirubin glucuronide is formed by the transfer of glucuronic acid from uridine diphosphate glucuronic acid (UDPGA) in the presence of the microsomal enzyme UDP-glucuronyltransferase (uridine diphosphate glucuronate glucuronyltransferase, E.C.2.1.17). On the basis of studies in experimental animals (Dutton, 1959), it is usually considered that deficiency of this enzyme is the main aetiological factor in causing hyperbilirubinaemia, but it has not been possible to confirm this hypothesis since a stable purified preparation of this enzyme has not been studied (Mowat and Arias, 1970).

An alternative hypothesis, that the hyperbilirubinaemia is due to a relative deficiency of UDPGA, correctable by ingesting uridine precursors such as aspartic acid and orotic acid, prompted the study of Matsuda and Shirahata (1966) who showed that in healthy term infants both aspartic acid and orotic acid lower serum bilirubin concentrations. The present observations were made on pre-term infants, in whom 'physiological' jaundice may be sufficiently severe to cause kernicterus, in order to determine whether the action of these agents might be of value in preventing serious hyperbilirubinaemia.

Methods

Observations were made on 34 healthy pre-term infants of known gestational age. All were without haemolytic disease, infection, respiratory distress, or congenital abnormality, and none was receiving drugs.

The infants, matched for sex, were allocated to three main groups of equal size who received orotic acid, glucose, or aspartic acid in equimolecular amounts in a double-blind fashion. Each group was subdivided by gestational age into three equal groups of 31 to 33 weeks; 34 to 36 weeks; and 37 to 39 weeks' gestation. In the most immature group of infants receiving orotic acid and glucose, observations on one female infant were incomplete and therefore not considered. Since gestational age was calculated from the date of onset of the mother's last menstrual period, only infants born to mothers who were certain of this date and whose menstrual cycles were regular were included in the study.

Infants in the study were fed according to a standardized feeding regimen involving 10% glucose feeds in the first 24 hours of life and the introduction of half-strength half-cream dried milk (Cow and Gate) within 36 to 48 hours followed by full-strength half-cream milk 48 hours later. Solutions of orotic acid, glucose, and aspartic acid (as magnesium aspartate) were made up to contain 130 mg, 125 mg, and 100 mg/per 12·5 ml, respectively. These were given twice daily with feeds, starting within 24 hours of birth, according to the following weight-based dosage schedule: 1·0–1·5 kg, 7·5 ml; 1·5–2·0 kg, 10·0 ml; 2·0–2·5 kg, 12·5 ml for a total of 12 doses.

Serum bilirubin levels were determined on the 2nd, 4th, 6th, and 8th day by the method of Lathe and Ruthven (1958). All values reported are of indirect-reacting bilirubin.

Results

The mean serum bilirubin values determined 2, 4, 6, and 8 days after birth follow a similar pattern in all three treatment groups, with a wide overlap in values between the groups. In female infants values were lower than in males, but this difference did not reach statistical significance (Table). Maximum serum bilirubin levels were found in the glucose-treated group on day 2 in females and on day 4 in males; on day 6 in the group receiving orotic acid; and on day 2 in those receiving aspartic acid. In contrast to the findings in other groups, mean serum bilirubin levels in male infants treated with aspartic acid fell from the highest value on the 2nd day. In this group of infants maximum serum bilirubin levels on days 4, 6, and 8 compared with the level on day 2, were significantly lower ($p<0·01$) than those in other groups. There were no other significant differences in serum bilirubin levels.