JAUNDICE IN A NEWBORN — A DIAGNOSTIC PROBLEM

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Neonatal jaundice and hyperbilirubinaemia are usually associated with haemolytic disease of the newborn due to rhesus incompatibility; that other causes have to be kept in mind in reaching a diagnosis is illustrated by the following case.

Case Record

A male child weighing 7 lb. 7 oz. was born in hospital and discharged in good condition. He was readmitted when 15 days old because of increasing jaundice of about one week's duration. On examination the baby was moderately jaundiced, with a temperature of 99.4°F ,and a pulse rate of 120/min. There was some conjunctivitis with lacrimation, but otherwise no abnormality was detected.

Pregnancy had been complicated by threatened abortion during the fifth month. Antepartum haemorrhage had occurred, and labour had been induced with buccal oxytocin.

The only other child in the family, the first born, is alive and well. A second male child died when 4 days old suffering from "deep jaundice".

The investigations that were carried out are tabulated in *Table 1*. On admission (Sept. 15), the haemoglobin was 10.7G/100 ml, P.C.V. 30%, reticulocytes 2.4%, normoblasts 2%. The blood smear showed a normocytic and fairly markedly hypochromic anaemia with poikilocytes and cell fragments and other irregularly contracted cells. Serum bilirubin was 18.2mg/100ml — this was indirect reacting. There was no biliburin, urobilinogen or urobilin in the urine. Coombs test was negative. Two das later the haemoglobin was 9.9 G/10ml, PCV 34%. After 8

TABLE I
Summary of investigations carried out

Date	*Hb*		*PCV*	*WBC*	*N*	*E.*	*B.*	*L.*	*M.*	*Retic* %	*S. Bil.r. mg/100 ml.*	*Bl Urea mg/100 ml*
	G/100ml	%	%	*per c.mm.*								
15.9	10.7	72	30	9500	30	2	2	58	2	2.4	18.2	
17.9	9.9	67	34	6300							11.4	
23.9	10.9	74	34	9200	12	—	—	80	8			20
26.9	11.1	75										
30.9	10.9	74	33									
4.10	11.4	77		10800								
8.10	8.7	59	27	9000								
14.10	11.1	75		8500								

days the Hb was still 10.9G/100ml, PCV 34%. The blood urea was 20mg/100ml. For the next 2-3 weeks the Hb remained at about 10-11 G/100ml in spite of blood transfusions of 60cc each on Sept. 18th and again on Oct. 10th.

The baby's blood was shown to be Group O Rhesus +. The mother was Group A Rhesus +. No antibodies were found in the mother's blood when she was retested three days after admission (18 days after birth).

G-6-P D Assay

Quantitative estimation of glucose-6-phosphate dehydrogenase (G-6-PD) was carried out using the test kit supplied by Boehringer (Mannheim). Assays of G-6-PD depend on the increase in absorbance which occurs at 340mμ when NADP is reduced to NADPH in the presence of glucose-6-phosphate — a reaction which is catalysed by the enzyme G-6-PD present in the red cells. Thus the change in optical density per minute is proportional to the amount of G-6-PD present in the red cells.

Haemolysates were prepared from the baby's blood as well as from its mother and father ,and the G-6-PD activity was assayed. *Fig. 1* shows the results. Curve 4 is a normal (control) reaction, and it can be seen that there is a considerable increase in O.D. over a ten minute period: the change in Optical Density per minute (O.D./min) was 0.005. Curve 3 was obtained from a haemolysate of blood obtained from the father, and again it is within the normal range (O.D./min = /.003). However, when the baby's blood was tested (curve 1) there was no activity at all, whereas the haemolysate from the mother (curve 2) showed very little activity (O.D./min = 0.0005), indicating a severe reduction of G-6-PD activity in the red cells.

From these findings it was concluded that the baby was suffering from a haemolytic anaemia due to G-6-PD deficiency inherited from the mother.

Discussion

Jaundice in the newborn often presents diagnostic problems. A practical

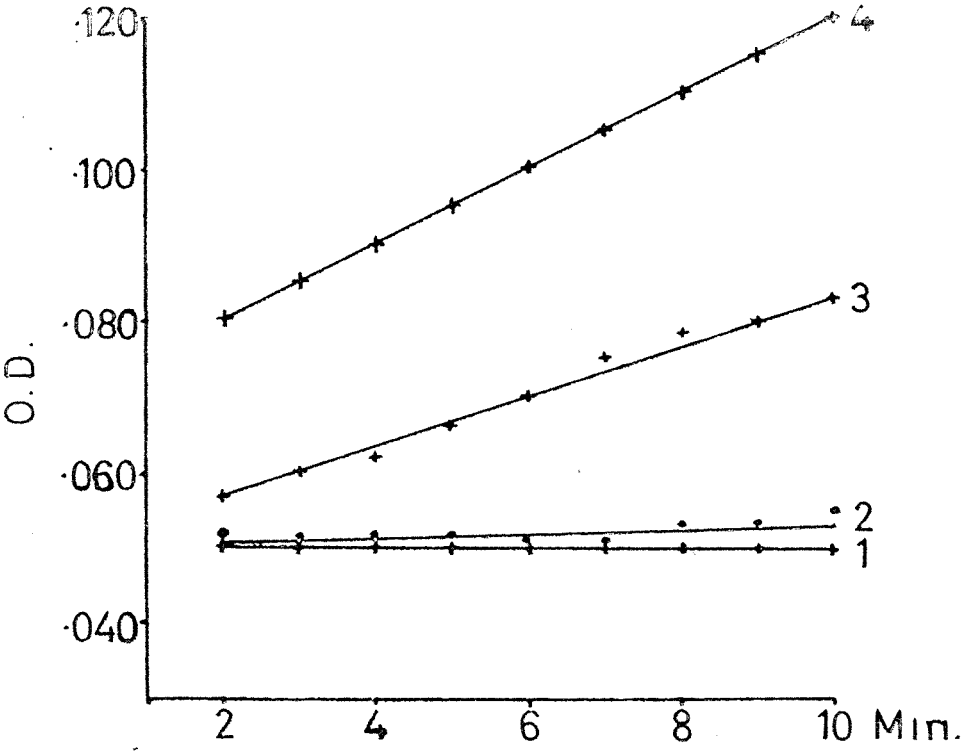

Fig. 1

TABLE II
Classification of Jaundice in the Newborn. (After Nelson, 1964)

Time of first appearance of Jaundice	*Examples*
A) At birth or within first 24 hours	*Erythroblastosis foetalis,* Cytomegalic inclusion dse, Cong. toxoplasmosis,
B) Jaundice on 2-3 day	*Physiologic,* severe hyperbilirubinaemia of the newborn, familial nonhaemolytic icterus.
C) After 3rd day and within first week	Septicaemia, Syphilis, toxoplasmosis, cytomegalic inclusion dse.
D) After first week	septicaemia, cong. atresia of bile duct, homologous serum hepatitis, herpetic hepatitis, idiopathic dilatation of common bile duct, galactosaemia, cong. haemolytic anaemia (spherocystosis) other haemolytic anaemias (thalassaemia, sickle cell dse., hereditary non spherocytic anaemia, haemolytic anaemia due to drugs, etc.
E) Persistent during the first month	Inspissated bile syndrome (following e.g. haemolytic dse. of the newborn, hepatitis, cytomegalic inclusion dse., toxoplasmosis.)

classification depending on the time of first appearance of the jaundice is given in *Table 2.* Jaundice due to G-6-PD deficiency usually appears in the first 2-4 days of life (Weatherall, 1960; Doxiadis and Valeas, 1964), and maximal hyperbilirubinaemia occurs during the 3rd-5th day (Zinkham, 1963; Doxiadis and Valaes, 1964). The jaundice may however appear during the first 24 hours (Doxiadis and Valaes, 1964), or as late as the 10th day of life (Shahidi, 1959; Zinkham, 1963).

The development of extreme hyperbilirubinaemia and even kernicterus in babies deficient in G-6-PD has been reported from all over the world (Valaes and coworkers, 1961, 1964; Weatherall, 1960; Smith and Vella, 1960; Segni, 1959; Panizon *et al.*, 1958). In Greece (Doxiadis *et al.*, 1961), Sardinia (Panizon, 1959), Malaya (Smith and Vella, 1960), and Thailand (Flatz *et al.*, 1963), G-6-PD deficiency is one of the major causes of severe neonatal jaundice, but in American negroes and in some non-Ashkenazi Jews, no cases of severe neonatal jaundice due to this cause were found (Zinkham, 1963; Szeinberg *et al.*, 1963). In Greece, Doxiadis and Valaes, (1964) found that over half of the cases of newborns suffering from jaundice not due to incompatibility were due to G-6-PD deficiency. Zanos-Mariolea *et al.* (1968) found that 25% of babies suffering from severe jaundice were G-6-PD deficient.

Not all G-6-PD deficient infants suffer from jaundice, however. It is probable that only about 4-5% of G-6-PD deficient infants have any severe degree of jaundice (Valaes, quoted by Zinkham, 1963; Fessas *et al.*, 1962). As the incidence of G-6-PD deficiency in Malta is about 2% (Cauchi, 1968), one can expect severe jaundice due to this cause in 1-2 per 1000 births. Although females heterozygous for the condition usually have milder G-6-PD deficiency, the degree of jaundice is not necessarily less. In fact there is no correlation between the severity of the G-6-PD deficiency and hyperbilirubinaemia (Zinkham, 1963). There is also no evidence that the

enzyme is qualitatively different (Kirkman *et al.*, 1965).

The mechanism of haemolysis in G-6-PD deficiency is not well understood. The enzyme occupies a key position in red cell metabolism, and its absence renders the cell more liable to haemolysis. A number of drugs and other substances such as, primaquine, sulphadiazine, sulphapyridin, trinitrotoluene, naphthaline, chloramphenicol, etc. (W.H.O. 1967) are known to produce haemolytic anaemia in persons that have G-6-PD deficiency, but jaundice in a newborn may occur in the absence of such agents given either to the baby or to the mother. 50% of G-6-PD deficient newborn babies who develop severe jaundice have not been exposed to drugs known to produce haemolysis in G-6-PD deficient individuals (Zanos-Mariolea *et al.*, 1968). Exogenous factors might be responsible for precipitating haemolytic anaemia in these infants (Weatherall, 1960; Smith and Vella, 1960) but search for such factors has so far been unsuccessful (Valeas *et al.*, 1961; Doxiadis *et al.*, 1961).

The risk of having a G-6-PD deficient child when one parent is affected can be predicted. As this condition is a sex linked characteristic, if the father is deficient, then the sons will be normal, and the daughters will be heterozygous for the condition. If the mother is affected, then 50% of the children will be affected, i.e. males will be hemizygous, while females will be heterozygous. The risk of having severe jaundice is much less than this, as already indicated. Accurate estimate of the probability of having a jaundiced child is rendered more difficult because G-6-PD deficient infants from some families and from some communities seem to run a higher risk of neonatal hyperbilirubinaemia than do other G-6-PD deficient infants (Fessas *et al.*, 1962; Doxiadis *et al.*, 1964; Freir, 1965). The likelihood of severe neonatal jaundice in the male G-6-PD deficient infant where there is a family history of severe neonatal jaundice due to G-6-PD deficiency may be as high as 50% (Fessas *et al.*, 1962).

In summary, therefore, a case of G-6-PD deficiency giving rise to severe jaundice in the first week of life has been described. As the condition is being recognised more frequently, one should think of G-6-PD deficiency in places like Malta where the incidence of the deficiency is fairly high whenever a case of jaundice not due to rhesus-incompatibility arises. The avoidance of drugs and other substances that are known to cause haemolysis may then prevent fatal kernicterus and other complications of severe jaundice of the newborn.

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