THE CLINICAL PICTURE OF GLUCOSE 6-PHOSPHATE DEHYDROGENASE DEFICIENCY IN EARLY INFANCY

BY

S. A. DOXIADIS AND T. VALAES

From the Paediatric Unit of the Children's Hospital 'Aghia Sophia', Athens, Greece

(RECEIVED FOR PUBLICATION MAY 11, 1964)

Cases of severe neonatal jaundice not due to incompatibility or prematurity but associated with glucose 6-phosphate dehydrogenase (G-6-PD) deficiency were described independently by workers in Italy (Panizon, 1959; Panizon and Meo, 1959; Panizon, 1960a, b; Segni, 1959) Singapore (Smith and Vella, 1960) and Greece (Doxiadis and Valaes, 1960; Doxiadis, Fessas, and Valaes, 1960; Valaes, Fessas, and Doxiadis, 1961). In a systematic study of a large group of infants with severe neonatal jaundice not due to incompatibility we presented conclusive evidence that there was an aetiological relation between G-6-PD deficiency and haemolysis leading to severe neonatal jaundice (Doxiadis, Fessas, Valaes, and Mastrokakos, 1961). Prior to these reports there was also mention of severe unexplained neonatal jaundice in the histories of many infants with congenital non-spherocytic haemolytic anaemia due to G-6-PD deficiency (Newton and Bass, 1958; Zinkham and Lenhard, 1959; Shahidi and Diamond, 1959). The above and other reports (Weatherall, 1960; Gilles and Arthur, 1960; Gaburro, Volpato, and Giaquinto, 1961; Lee, Tink, Robin, and Harley, 1961; Martoni, 1962; Babin and Salvioli, 1962; Jim and Chu, 1963; Flatz, Sringam, and Komkris, 1963) have firmly established G-6-PD deficiency as a cause of severe neonatal jaundice. The incidence of this clinical manifestation among the G-6-PD deficient newborns varies widely from one ethnic group to the other. Thus while in Greece (Doxiadis et al., 1961), Sardinia (Panizon, 1959; Panizon and Meo, 1959; Panizon, 1960a, b), 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, in the American Negroes and in some non-ashkenazi Jews with high frequency of G-6-PD deficiency no cases of a severe neonatal jaundice due to this cause were found (Zinkham, 1963; Szeinberg, Oliver, Schmidt, Adam, and Sheba, 1963). We found that in Greece the cases of severe neonatal jaundice were not evenly distributed among the G-6-PD deficient newborns, but that there was an accumulation of such cases in some families (Fessas, Doxiadis, and Valaes, 1962). The analysis of our material suggested that a second probably genetic factor was necessary for the manifestation of neonatal jaundice in the G-6-PD deficient infants. The absence of this second factor in some of the ethnic groups may be the explanation for the lack of neonatal jaundice among their G-6-PD deficient infants.

As up to now clinical details of this type of jaundice have been published for isolated cases only, we considered that it would be of interest to present our experience of the clinical aspects of G-6-PD deficiency in early infancy based on 135 cases. Other aspects of the cases studied will be published later.

Material and Methods

The material of the present study consists of: (a) all (112) newborns or young infants seen by us with severe jaundice or anaemia and found to be G-6-PD deficient; and (b) 23 infants who were not seen by us in the neonatal period; 12 were seen later with severe sequelae of kernicterus for which no cause other than G-6-PD deficiency could be found; the remaining 11 died during the neonatal period with symptoms of kernicterus, and the investigation of the family made it very likely that this enzyme deficiency was the cause of their jaundice. The cases seen at the beginning of our study were investigated at the Newborn Unit of the Alexandra Maternity Hospital and the infants seen from the beginning of 1962, were examined at the Paediatric Unit of the Children's Hospital 'Aghia Sophia'.

For the assessment of the G-6-PD activity we used the method of Motulsky and Campbell as described in a previous publication (Doxiadis et al., 1961). Serum bilirubin was estimated by the method of Malloy and Evelyn (1937).

Results

Table 1 shows the total of our material divided according to the main clinical manifestation. It is clear that there is an overwhelming preponder-
DOXIADIS AND VALAES

Table 1

<table>
<thead>
<tr>
<th>CASES WITH G-6-PD DEFICIENCY AND CLINICAL MANIFESTATIONS IN INFANCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Severe neonatal jaundice not due to incompatibility</td>
</tr>
<tr>
<td>Marked anaemia but no severe jaundice</td>
</tr>
<tr>
<td>Severe jaundice with G-6-PD deficiency and incompatibility or prematurity</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>NEWBORNS WITH SEVERE JAUNDICE DUE TO G-6-PD DEFICIENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Kernikterus not treated</td>
</tr>
<tr>
<td>Kernikterus treated by E.T.*</td>
</tr>
<tr>
<td>Severe jaundice treated by E.T.</td>
</tr>
<tr>
<td>Severe jaundice not requiring E.T.</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

* E.T. = exchange transfusion

ance of cases of severe neonatal jaundice, only 5 out of the 135 infants showing no severe jaundice but only anaemia. This is not necessarily representative of the true picture, since cases of jaundice were more likely to be brought to our notice because of our well-known interest in this condition. Moreover jaundice is a more alarming symptom at this age than anaemia and is more likely to lead to admission. Of the 112 babies seen by us during their illness, 87 were boys and 25 were girls, which is not surprising in view of the sex-linked character of this enzyme deficiency. On the other hand this may not represent the true sex incidence because, though the deficient males are easily detected, the heterozygous female may escape detection. Of the 25 females, the enzyme activity was as low as in the males in 4, intermediate values were found in 9, and normal values were found in the remaining 12 with the method used, and their heterozygous state was inferred because the fathers were enzyme deficient.

In Table 2 the group of newborns with severe jaundice is divided according to the main clinical manifestation and treatment. In the cases with kernikterus not treated are included those infants sent to us either in a moribund state or at the stage of the fall of the serum bilirubin, when no benefit could be expected from exchange transfusion. The cases with kernikterus treated by exchange transfusion included the infants in whom, though there was at the time of admission unequivocal evidence of central nervous system involvement, it was thought that further damage might be prevented by exchange transfusion. In the third group exchange transfusion was considered necessary to prevent the development of kernikterus. The indication for exchange transfusion was the level of serum bilirubin. The level considered as critical had to be changed in 1960 from 20 mg./100 ml to 25 mg./100 ml., following the introduction of a new bilirubin standard in early 1959 and the experience gained after the change of the standard. Finally the infants considered as having severe jaundice though not needing exchange transfusion had maximal serum bilirubin recorded of 16 mg./100 ml. or more.

By direct questioning of the doctors or parents we were able to find that 27 of the 90 infants were exposed to known exogenous agents possibly eliciting or increasing haemolysis. In 11 infants this agent was naphthalene inhalation. Details of these cases have been already published (Valaes, Doxiadis, and Fessas, 1963). The mother of one infant received an unknown dose of quinine by mouth during induction of labour. Finally the remaining 15 infants received a synthetic vitamin K analogue (menadione sodium bisulphate). In only one was the total dose as high as 30 mg., given over 3 days, in 12 the dose ranged between 2 and 10 mg. and in the remaining two it was unknown. The preparation was given intramuscularly in all but one who received it by mouth. The vitamin K analogue was given to two infants immediately after birth, and in the remaining infants after the onset of jaundice and before the appearance of kernikterus or exchange transfusion. This delayed administration of vitamin K is explained by the erroneous view of some doctors that it exerts some therapeutic effect on neonatal jaundice.

Of the 18 infants with kernikterus not treated by exchange transfusion, 8 showed, at some time in the
course of their hyperbilirubinaemia, a conjugated bilirubin value above 5 mg./100 ml. The number of similar cases among the 55 infants treated with exchange transfusion was 3.

Our material includes 23 infants not seen by us during the neonatal period. Of these, 12 (6 males and 6 females) were examined later and had sequelae of kernicterus and G-6-PD deficiency without any other explanation for their severe neonatal jaundice. Eleven cases came to our notice after death, when, on admission for another delivery, their mother gave the history of a previous child dying with symptoms of kernicterus. All 8 males of this group had one enzyme-deficient sib, and their mothers had either complete or intermediate G-6-PD deficiency. The 3 females of the group had G-6-PD deficient fathers and were necessarily heterozygous for the abnormal gene. In the whole group of 23 infants we could find an exogenous factor in 7.

G-6-PD deficiency was present in another 17 infants who had also an additional cause for neonatal jaundice. One had haemolytic disease of the newborn due to Rhesus incompatibility and had an early exchange transfusion. Foeto-maternal ABO incompatibility was present in another 10 cases (of these 2 had kernicterus on admission). Serological proof of ABO haemolytic disease was not sought, but in only 4 of them did the jaundice appear in the first 24 hours. Finally 6 infants were premature.

Five male infants had marked anaemia and no significant jaundice. Two of them had been exposed to naphthalene inhalation and are described in another publication (Valaes et al., 1963). Another two were found to have severe anaemia in the first two months in the absence of any of the known causes (see Appendix, Case 6). Finally one infant showed the typical clinical and haematological picture of chronic non-spherocytic haemolytic anaemia. It is worth noting that a previous male sib died at the age of 45 days from the same condition and that the present patient had no severe neonatal jaundice. In all our material this is the only family with this clinical manifestation.

The importance of early detection and treatment of severe hyperbilirubinaemia makes necessary a detailed description of the main features of neonatal jaundice due to G-6-PD deficiency. The description is based on the 90 infants (70 boys and 20 girls, Table 2) seen by us during the first week of life.

Fig. 1 shows the day of life at which jaundice was first noticed, the information being obtained in most cases from the parents, midwife, or attending doctor. It can be seen that in the majority of newborn infants the jaundice was noticed in the second and the third day of life. However, in 12 infants jaundice was first noticed in the first 24 hours. Equally important is the appearance of jaundice after the fourth day in a few infants, even in the absence of any known exogenous factor.

Fig. 2 shows the age at which the hyperbilirubinaemia reached a ‘decisive point’. In some infants this meant the day when symptoms of kernicterus appeared, in others the age at which we intervened by exchange transfusion, and, finally, in those with
jaundice not requiring exchange transfusion, the day of the peak of the serum bilirubin curve. For most infants this decisive point was on the third, fourth, and fifth day of life. However, it should be noted that one infant developed kernicterus as early as the second day, and in another six serum bilirubin reached the critical level for exchange transfusion at the same age. On the other hand, in 14 newborn infants, the decisive point was reached after the first week, four of them developing kernicterus on the ninth, tenth, or eleventh day.

Fig. 3 shows the pre-exchange or maximal serum bilirubin values. Of the 32 infants with serum bilirubin values of 35 mg./100 ml or more, only nine had at the time no signs of central nervous system involvement. Follow-up study is not yet completed. At the other end of the scale five infants developed kernicterus with maximal serum bilirubin values recorded of 25 mg./100 ml or less. These infants were admitted when the serum bilirubin was falling and it is likely that higher levels had been attained before.

In those infants in whom we were able to follow the course of serum bilirubin the rate of its rise varied widely. Thus, while in some a rise of 10 mg./100 ml in 24 hours was noted, in others the rise was much slower, not exceeding 2-3 mg./100 ml in 24 hours. When the rise of serum bilirubin was not interrupted by exchange transfusion it continued for four to six days. The shape of the curve was regular, without any secondary rise, at least in the absence of exogenous factors.

Fig. 4 shows the pre-exchange or minimal haemoglobin values recorded in relation to age. While very few of the infants were found to have frank anaemia in the first week of life, those that were not treated and whom we were able to follow in the second week showed low haemoglobin values.

Discussion

In Greece, as in some other countries, in a substantial number of full-term newborns with jaundice either leading to kernicterus or necessitating an exchange transfusion, no foeto-maternal blood incompatibility is present. Thus in our material of 80,380 consecutive full-term infants the incidence of exchange transfusion was 1:23/1000 for Rhesus haemolytic disease, 1:68/1000 for ABO incompatibility, and 1:42/1000 in those without incompatibility. Moreover, among 47 full-term newborns sent to us too late and with established kernicterus, in 37 there was no Rhesus or ABO incompatibility. Since we started testing all newborns with jaundice for the G-6-PD activity of their red cells we found that over half of the cases with no incompatibility were G-6-PD deficient. Still more impressive are the figures of the infants admitted with kernicterus. In this group, 80% of those tested were G-6-PD deficient. From
all this it becomes evident that, in some countries at least, severe neonatal jaundice due to G-6-PD deficiency is, because of its frequency, of great practical importance.

The present work shows that the main clinical manifestation of G-6-PD deficiency in the neonatal period is jaundice. For the development of this type of jaundice, as with any other jaundice in the first week of life, two factors usually contribute; increased rate of haemolysis and decreased ability of the liver to conjugate and excrete bilirubin. This decreased ability is taken for granted in all newborn infants, though the degree may differ from one infant to the other. The propensity to haemolysis of the G-6-PD deficient red cells makes it likely that the neonatal jaundice of the G-6-PD deficient infants is due to increased red cell destruction. Though in individual cases proof of haemolysis was not always easy to obtain, in our material as a whole there was enough evidence in favour of increased haemolysis. In many cases the rise of serum bilirubin exceeded 5 mg./100 ml. in 24 hours. This was particularly obvious in the newborn infants who developed kernicterus or required exchange transfusion in the first three days of life. Such a rapid rise is considered as evidence of haemolysis (Zuelzer and Brown, 1961; Valaes, 1963), since it cannot be due to liver immaturity only. Additional evidence of haemolysis was provided by the low haemoglobin values in some infants or by the progressive fall in all those not treated by exchange transfusion. On the other hand the destruction of a red cell mass sufficient to produce hyperbilirubinaemia may not be reflected in the haemoglobin concentration, because of the high cord haemoglobin values and the haemoconcentration of the first days of life. It should also be mentioned that in many cases morphological changes of the red cells (fragmentation, pyknocytosis, Heinz body formation) were highly suggestive of haemolysis.

The onset of haemolysis varied widely as can be inferred from the time of appearance of jaundice. For those whose jaundice became obvious in the first day of life, it was not possible to say whether haemolysis started before or after birth since no cord blood was examined. When the natural course was not interrupted by exchange transfusion the proportion of the red cell population destroyed, as judged by the fall of haemoglobin, varied widely.

The haemolysis did not occur in waves in the absence of exogenous factors and was self-limiting. This may be inferred from the absence of secondary rises of the serum bilirubin and eventual disappearance of the jaundice. This observation suggests that the stress affecting the metabolism of the deficient red cells does not operate continuously. None of the infants with severe neonatal jaundice developed later chronic haemolytic anaemia. The duration of the stress cannot be assessed because a stress of a certain intensity, after destroying the cells of a certain age, will become ineffective, as has been shown in primaquine-induced haemolysis (Kellermeyer, Tarlov, Schrier, Carson, and Alving, 1961). The varying proportion of the red cell population destroyed may mean either a differing intensity of the stress or a varying susceptibility of the red cells.

In the infants in whom an exogenous factor was present this constituted the above-mentioned stress. In the babies exposed to naphthalene inhalation the metabolites of naphthalene were the factor eliciting the haemolysis and the mechanism has been well studied (Zinkham and Childs, 1958). A similar mechanism was operating in the cases receiving another naphthoquinone derivative, menadione sodium bisulphate (vitamin K analogue). In our material the dose received fell, with one exception, within the range found safe for American Negro G-6-PD deficient infants (Zinkham, 1963). It is impossible to state with certainty if the small doses received by our newborn infants influenced the course of their haemolysis. Of the 15 who received a vitamin K analogue, 9 were admitted with kernicterus, a higher proportion than in the rest of our material. This, however, should not be taken as necessarily indicating more severe haemolysis but perhaps later referral. The doctors who unnecessarily gave vitamin K analogues were those that were more likely to delay referral of their cases to hospital. In spite of this we cannot accept Zinkham's (1963) conclusions regarding the safety of small doses of vitamin K analogues in all G-6-PD deficient newborns, as the subjects of his study, American Negro newborns, do not as a group exhibit severe neonatal jaundice as a manifestation of G-6-PD deficiency. In view of this uncertainty we think that in countries with neonatal jaundice due to G-6-PD deficiency, routine administration of vitamin K analogues for the prevention of such a rare and easily treated condition as haemorrhagic disease of the newborn should not be recommended.

In more than half of our cases no known exogenous factor could be found. The likelihood that such factors were present but not detected is very small, because in most cases we were able either to observe personally or obtain accurate information as to the circumstances and drugs of the perinatal period for mother and baby. Therefore, the nature of the stress eliciting haemolysis is at present a matter of speculation. Whatever the nature of the stress, it must be limited in time and probably linked to the metabolic changes occurring during and after delivery. Of
these changes hypoglycaemia is a likely possibility though difficult to prove. It should be noted that, as we have shown (Fessas et al., 1962) for the development of severe neonatal jaundice in the G-6-PD deficient infants, a second factor, probably genetically determined, is necessary. Whether this factor increases haemolysis or is related to the excretion of bilirubin is at present unknown.

From a practical point of view it is important for all doctors practising in countries where this type of jaundice occurs to be aware of the following clinical aspects. In the majority of infants the jaundice appears on the second and third day of life and therefore cannot be distinguished from the so-called physiological jaundice. There are also cases with a later onset and a rise of serum bilirubin continuing well into the second week of life and causing kernicterus as late as the eleventh day. To prevent such a development the doctor should keep a continuous watch on the height of serum bilirubin until such time as a steady fall is noticed. Neither the day of onset of the jaundice nor the day of life of the infant can be relied upon when forecasting a safe course. Having seen infants developing kernicterus in the second week of life we no longer rely on the maturation of the blood-brain barrier to protect the cells of the nervous system against the toxic effects of hyperbilirubinaemia (Valaes, 1961).

Though differences may exist regarding the critical level of serum bilirubin for the development of kernicterus, we consider that the indication for exchange transfusion in cases of jaundice due to G-6-PD deficiency is the height of serum bilirubin independent of the age of the infant. In our experience the same policy should be followed in all cases of severe neonatal hyperbilirubinaemia independently of aetiology.

Since in our material most infants came to our notice after they had developed a severe jaundice, only then being found to be G-6-PD deficient, it has not been possible so far to detect in advance those G-6-PD deficient infants who are likely to develop severe jaundice. We are at the present time trying to assess the value of laboratory methods for this purpose.

The finding of G-6-PD deficiency by the qualitative or quantitative method in a newborn serves only as a warning signal, as also does a family history of favism or drug-induced haemolysis. At present the only point of predictive value is a family history of severe neonatal jaundice due to G-6-PD deficiency, because our material has shown that the likelihood of severe neonatal jaundice in the male G-6-PD deficient infants of these families is approximately 50% (Fessas et al., 1962).

Summary

The main clinical features in 135 infants with severe jaundice or anaemia due to G-6-PD deficiency are described. In 130 of the infants jaundice was the main clinical manifestation. Of the 112 infants studied in the neonatal period 87 were boys and 25 girls, and in 33 kernicterus was present on admission. 12 infants were seen later with sequelae of kernicterus and 11 died from this cause, and only their families were studied. Among the 135 infants, 36 were either exposed to naphthalene inhalation or received vitamin K analogues. In the remaining cases no exogenous haemolytic factor was detected.

In the majority, jaundice appeared on the second and third day and reached a decisive point between the third and fifth day of life. In a few cases jaundice appeared later, and four infants developed kernicterus after the first week of life.

Part of this work was supported by a research grant from the Association for the Aid of Crippled Children.

We are indebted to Doctors A. Arseni, M. Pavlatou, Ph. Fessas, and A. Karaklis for many of the laboratory data and for their advice.

References


ARCH DIS CHILD: first published as 10.1136/adc.39.208.545 on 1 December 1964. Downloaded from http://adc.bmj.com/ on May 24, 2022 by guest. Protected by copyright.
G-6-PD DEFICIENCY IN EARLY INFANCY


Appendix

Illustrative Cases Reports

Case 1. This male infant was born at term by normal delivery on January 20, 1963, in a private nursing home, birth weight 3,220 g. Jaundice was noticed on the fourth day and had increased only slightly on the sixth day when the infant was discharged home. According to the parents the jaundice did not increase and the behaviour of the baby was normal up to the tenth day. In the morning of this day intense jaundice was noticed and the infant refused to suck. On admission at noon on the tenth day the infant was deeply jaundiced, hypotonic, with absent Moro's and grasp reflexes and with superficial, irregular respirations and slight cyanosis. It was thought that the baby was in the terminal stage of kernicterus. At 10 p.m. of the same day the picture had changed. Hypertyon with opisthotonus and extensions of the limbs was present. The respirations were normal and the cry strong but shrill. No exchange transfusion was performed, as on admission it was thought that the infant was going to die. When later the picture changed the serum bilirubin was also on the decline. The infant was discharged on the sixteenth day still with hypertyon and opisthotonus but feeding well.

Exposure to naphthalene was excluded. Neither the mother nor the infant received any drugs. The mother had not ingested vicina fava.

Laboratory investigations. Mother group B, Rhesus positive, and the infant group O, Rhesus positive. The direct Coombs test was negative. The rest of the results are given in Table A.

The infant and his brother, who had had no significant neonatal jaundice, were found to be G-6-PD deficient. The mother had intermediate and the father normal enzyme activity.

Case 2. A female infant was born on January 18, 1963, in a nursing home on the island of Corfu, birth weight 3,500 g. On the second day of life jaundice was noticed. Next day the jaundice was intense and the infant was sent to us. On admission, at the age of exactly 3 days, she was intensely jaundiced and equivocal signs of kernicterus were present. There was no hepatosplenomegaly. In spite of immediate exchange transfusion the signs of kernicterus were more definite the next day and persisted for another 3 days. At the age of 6 months she was reported to be retarded in her motor development. An older sister had no neonatal jaundice and is developing normally. The mother received no drugs during the perinatal period and exposure to naphthalene was excluded.

Laboratory investigations. Mother and infant were group O Rhesus positive. The direct Coombs test was negative.

On admission haemoglobin 17·8 g. 100 ml. Reticulocytes 6·4%. Heinz bodies present in 7% of the red cells. The course of the serum bilirubin values is shown in Fig. 5. The G-6-PD activity of the mother and the infant were in the intermediate range. The father was normal.

Table A

<table>
<thead>
<tr>
<th>Day of Life</th>
<th>HAEMATOLOGICAL DATA FOR CASE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noon 10 10 p.m.</td>
<td>Serum bilirubin (mg. 100 ml.) 41-6 40-4</td>
</tr>
<tr>
<td>11</td>
<td>28-6</td>
</tr>
<tr>
<td>13</td>
<td>12-6</td>
</tr>
<tr>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Copyright. Downloaded from http://adc.bmj.com on May 24, 2022 by guest. Protected by
DOXIADIS AND VALAES

FIG. 5.—Course of serum bilirubin values in Case 2. Arrow indicates exchange transfusion.

Case 3. A male infant was second of binovular twins born at term on December 2, 1962, at a hospital in Athens birth weight 2,500 g. Slight jaundice appeared on the second day and was moderate when the infant left the hospital on the eighth day. Next day the jaundice increased and was deep on the tenth day when he was admitted to 'Aghia Sophia'. There were no signs of kernicterus and no hepatosplenomegaly. Exposure to naphthalene, drugs, or vicia fava was excluded. The first twin, weighing 2,800 g., had asphyxia neonatorum and respiratory distress for the first hours. He did not develop jaundice.

Following exchange transfusion hyperbilirubinemia subsided rapidly and the baby was free of jaundice on the thirteenth day when he was discharged.

Laboratory investigations revealed the following blood groups: mother O, Rh positive; father B, Rh positive; first twin B, Rh positive; Second twin O, Rh positive.

On admission, haemoglobin 15·2 g./100 ml.; reticulocytes 0·4%; Heinz bodies 4·2%; spherocytes 2·3%; pyknocytes 1·7%; schistocytes 1%; serum bilirubin 37 mg./100 ml. total; direct 4·6 mg./100 ml.

On the same day the first twin had a haemoglobin level of 13·0 g. 100 ml.; reticulocytes 0·4%; no Heinz bodies, and no spherocytes; pyknocytes 1·8%, and schistocytes 1·2%. The results of the assessment of G-6-PD activity are shown in the family tree (Fig. 6).

Case 4. This male infant was born at home on February 13, 1960, after a normal delivery at term. His birth weight was 3,000 g. Two previous male sibs had no neonatal jaundice and are alive and well, while a female born prematurely died at the age of 10 days. The patient developed slight jaundice at the end of the first 48 hours.

The family doctor prescribed menadione sodium bisulphate 2 mg. to be given by mouth every 8 hours. Three doses were given altogether. The jaundice gradually increased and on the fifth day was extremely deep and the infant could not take his feeds. On admission the same day unequivocal signs of kernicterus were present.

Laboratory investigations on mother and infant showed they were group O, Rh positive. The direct Coombs test negative.

On the fifth day serum bilirubin total was 49·7 mg./100 ml.; sixth day total was 52·4 mg./100 ml. and direct was 23 mg. Haemoglobin was 18 g./100 ml. Reticulocytes 2·1%, and Heinz bodies negative. On the eighth day total serum bilirubin was 22 mg./100 ml. and direct was 6·4 mg. Haemoglobin was 14·4 g. 100 ml.

The father, the mother, and the two previous male sibs showed normal enzyme activity. The patient was found to be G-6-PD deficient.

At the age of 3½ months he was admitted to another hospital with hyperpyrexia. He was given an injection of a pyrazolone derivative following which severe haemolysis with haemoglobinuria, extreme anaemia (haemoglobin 3·8 g.), and uraemia appeared and the infant died four days later.

Case 5. All the three male infants in this family exhibited severe neonatal jaundice. The first infant was born at term in 1956, and died on the 4th day with symptoms of kernicterus. The second infant was born

<table>
<thead>
<tr>
<th>TABLE B</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAEMATOLOGICAL DATA FOR CASE 6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day of Life</th>
<th>4</th>
<th>19</th>
<th>40</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g. 100 ml.)</td>
<td>16·8</td>
<td>12·8</td>
<td>5·2</td>
<td>11·8</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>38</td>
<td>38</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>5·4</td>
<td>5·4</td>
<td>5·4</td>
<td>5·4</td>
</tr>
<tr>
<td>Pyknocytes (%)</td>
<td>1·1</td>
<td>0·4</td>
<td>2·8</td>
<td>2·8</td>
</tr>
<tr>
<td>Heinz bodies (%)</td>
<td>No</td>
<td>No</td>
<td>12</td>
<td>No</td>
</tr>
</tbody>
</table>

FIG. 6.—Family of Case 3. Results of assessment of G-6-PD activity. E.T., exchange transfusion.

FIG. 7.—Family of Case 5. Results of assessment of G-6-PD activity. F, favism; K, kernicterus; J, severe neonatal jaundice; E.T., exchange transfusion.
in Alexandra early in 1961, birth weight 2,900 g. Jaundice appeared on the second day with a maximum serum bilirubin value of 16·3 mg./100 ml. on the fourth day. The third infant was also born in Alexandra in May 1962, birth weight 3,450 g. Slight jaundice appeared on the second day but next morning the jaundice was marked and the serum bilirubin had risen to 30·3 mg./100 ml. Two hours later the serum bilirubin of the pre-exchange specimen was 33·7 mg./100 ml. Following the exchange transfusion the jaundice subsided rapidly. At the age of 18 months his development was normal and neither he nor the second child had any haematological abnormality.

The mother had an attack of favism when 12 years old, her father also had two attacks of favism. The blood groups of the family are as follows. Mother: group O, Rh positive; father: group A, Rh positive; second child: group A, Rh positive; and third child: group O, Rh positive.

The results of G-6-PD activity are shown in the family tree (Fig. 7).

Case 6. Male infant born on December 20, 1962, in a private nursing home four weeks before term. His birth weight was 2,400 g. He was transferred to the premature baby unit of Aghia Sophia. Jaundice appeared on the second day and remained moderate throughout the first week of life. The maximum serum bilirubin value was only 12·6 mg./100 ml. After the first week the jaundice gradually subsided and the infant was free of jaundice at the end of the second week.

When aged 40 days pallor was noticed and a low haemoglobin was found. He received a transfusion of 120 ml. sedimented red cells and the subsequent course was uneventful. At this age his weight was 3,300 g. He received no other drugs apart from 25 mg. vitamin C daily from the 20th day of life and vitamins A and D from the 35th day.

Laboratory investigations are set out in Table B.

The infant was found to be G-6-PD deficient, his mother showed intermediate and his father normal enzyme activity.