THE CLINICAL ASSESSMENT OF HAEMOLYTIC DISEASE
OF THE NEWBORN

BY

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There can be little doubt that at the present stage of our knowledge exchange transfusion is the best method of treating haemolytic disease of the newborn, at least in moderate and severe cases. Recently this viewpoint has been conclusively confirmed by widely based and controlled trials of British workers (Mollison and Walker, 1952; Armitage and Mollison, 1953); their results showed that the mortality of erythroblastotic infants treated by simple transfusions was three times that of those treated by exchange transfusion. In previous years, however, there was a considerable difficulty in differentiating those infants, in whom exchange transfusion was necessary, from those who would not require this radical procedure or any treatment at all. In fact, exchange transfusion is a preventive operation and must be considered soon after birth, i.e., at a time when only severely affected infants show manifest signs of haemolytic disease, most appearing clinically normal. Moreover, the serological findings have appeared to be by no means a reliable index of the post-natal course of the haemolytic disease. The unpredictable prognosis and the relative safety of exchange transfusion made many workers prefer to perform it even in infants who would probably recover without such a procedure. This is not an ideal trend of events and it is obvious that the early and reliable assessment of prognosis in any individual case is essential for the correct treatment.

The available methods of assessing haemolytic disease of the newborn consist of pre-natal control of pregnant women and the examination of newborn infants immediately after birth.

Pre-natally, there are two main points of study: the obstetrical history and the serological findings in the mother.

The occurrence of an adequately proved case of haemolytic disease of the newborn in a sensitized woman is almost always followed by the delivery of a more or less affected infant, unless its blood is compatible with maternal antibodies. Most authors assume that in any one family the prognosis of haemolytic disease gets worse in successive Rh-positive infants. Recently Davies, Gerrard and Waterhouse (1953) suggest, on the basis of statistical analysis, that there are two main groups of sensitized women. One, smaller group, tends to have severely affected infants in all successive pregnancies, and the other group tends to deliver infants with only a mild form of the disease. This observation seems to be in agreement with the frequent finding that in some families several mildly affected infants are successively born without an apparent increase in the severity of the disease. On the other hand, the occurrence of a severe form, i.e., stillbirth, usually signifies an unfavourable prognosis for future births.

The relation between the titre and type of maternal antibodies and the severity of the infant's disease has frequently been studied, and some workers still believe that the level of albumin antibodies is the chief factor determining the prognosis and therefore the treatment (Wiener and Wexler, 1949). There is, however, almost general agreement that the prognostic value of serological findings in the mother is somewhat slight: mothers with a high titre of antibodies have the higher probability of delivering an affected child, but exceptions are frequent and interfere with a reliable prognosis in any individual way.

In summary, at the present time it is not possible to predict the course of haemolytic disease on the basis of prenatal examination or even to prove actual damage of the foetus, with some exceptions, for example, the x-ray picture of hydrops foetalis.* The value of antenatal control lies in foreseeing the possibility of the haemolytic affection in the newborn. Thus, at birth all measures to confirm the diagnosis can be ready and adequate treatment undertaken within a few hours of birth.

* Dr. Čech, of our obstetrical staff, has shown that advanced haemolytic anaemia of the foetus is frequently accompanied by a continuous murmur in the foetal heart sounds. This finding in a sensitized pregnant woman can be very useful in deciding delivery before term (Čech, 1953).
After birth haemolytic disease of the newborn can be proved by serological, laboratory and clinical methods.

The finding of blood incompatibility between mother and infant is essential and in 90% of cases the typical combination of Rh-negative mother and Rh-positive child is found. However, the finding of the Rh-identity between mother and infant does not exclude the presence of haemolytic disease of the newborn. The possibility of the blocking effect should be borne in mind, for it means severely affected infants and is probably more frequent than the often quoted cases of incompatibility in Rh-subgroups.

The direct Coombs test is universally accepted as the most sensitive proof of passive immunization in the newborn infant. Its reliability is so high that a positive test can be identified with the presence of haemolytic disease of the newborn. In clinical practice, a negative Coombs test rules out the possibility of haemolytic disease due to Rh incompatibility. On the other hand, it is positive in a certain number of cases without any detectable signs of haemolysis and in mild forms of affection as well. Thus, its value in determining the treatment is to some extent limited.

The aim of laboratory and clinical examination is to prove the basic pathological disturbance, i.e., rapid destruction of red blood cells, and to judge its intensity. As Mollison and Cutbush (1949) have shown, the chief features of abnormal haemolysis, haemolytic anaemia and raised bilirubin level, are present at the end of pregnancy in all cases of haemolytic disease, but they are usually obscured by haemoconcentration and 'physiological' hyperbilirubinaemia of the post-natal period. They stressed the importance of examination of the cord blood.

Mollison and Cutbush (1951) have also shown the close relationship between the haemoglobin concentration in cord blood and the infant's chance of survival. The survival rate falls parallel with the decreasing haemoglobin level, an almost ideal sigmoid curve being the graphical expression. The high prognostic significance of haemoglobin concentration can be adequately explained since this is an index of the anaemic hypoxia to which the foetal tissues have been exposed up to the time of delivery. If permanent damage to vitally important tissues is already present at birth, the fate of the newborn infant can be only little changed by any later treatment.

The bilirubin level is always increased in the cord blood of affected children, but its prognostic significance is not so clear as that of the haemoglobin concentration. Mollison and Cutbush (1951) suggest that the prognosis cannot be more accurately predicted from haemoglobin and bilirubin concentrations together than from haemoglobin level alone. This conclusion is undoubtedly correct, if we consider the simple prediction of death or survival in a series of adequately treated children. Nevertheless, an increase of the bilirubin level in cord blood indicates an increased rate of destruction of red cells and the likelihood of the newborn infant being affected by severe hyperbilirubinaemia and perhaps developing kernicterus. This potential danger is usually prevented by exchange transfusion and the real prognostic significance of hyperbilirubinaemia is thus obscured. Nevertheless, it may be very useful in deciding on the necessity of exchange transfusion in borderline cases, where the haemoglobin concentration alone is not an entirely reliable guide (Mollison and Cutbush, 1951).

The assessment of a case is completed by the usual clinical and haematological examination. Definite anaemia in the capillary blood confirms the haemolytic process, when other causes of anaemia, for example, bleeding, are excluded. An increased number of nucleated red cells strongly supports the diagnosis of haemolytic disease of the newborn. Pallor, hepatosplenomegaly and early deep jaundice are the common clinical signs of the disease. The assessment of a case in which the examination of the cord blood has been omitted is based on these far less reliable features.

The Present Series

All pregnant women registered with the pre-natal clinic of the Research Hospital in Prague were tested for blood grouping, and Rh-negative patients were followed throughout pregnancy for the development of antibodies. The condition of every isoinmunized woman was analysed before and after birth by the methods described, but the final decision as to prognosis and treatment was based on the estimation of the haemoglobin and bilirubin concentrations in the cord blood.

Haemoglobin was determined by drawing 0.25 ml. of cord blood by pipette into 5 ml. of 0.1% NaCO₃. The resulting solution of oxyhaemoglobin was read in a Leitz photometer using a green filter (Nr. 550). The method is very simple and reliable and is the usual method of haemoglobin determination in our hospital.

Serum bilirubin was determined using a modification of the usual diazo method without caffeine.

The normal range of haemoglobin and bilirubin concentrations was determined in the cord blood samples of 150 normal newborn infants. The mean
haemoglobin concentration was 16-06 g./100 ml. (S.D. 1·43 g./100 ml.). Values below 12 g./100 ml. were considered definitely abnormal. The mean bilirubin concentration was 1·68 mg./100 ml. (S.D. 0·5 mg./100 ml.), the level of 3 mg./100 ml. being considered the upper limit of normal values. At the beginning of our work levels of 11·5 g. haemoglobin and 4 mg. bilirubin were assumed to be borderlines of normal values, but this opinion was corrected by further experience.

In our series are included 114 clearly isoimmunized women, observed from May, 1950, to May, 1954. Women without conclusive proof of isoimmunization, i.e., those with only traces of antibody or with a transient finding of low titre antibodies, especially during the first pregnancy, were excluded.

The values of cord haemoglobin and bilirubin concentration of newborn infants are plotted against one another in Fig. 1. The values of Rh-negative infants are excluded for the sake of clarity.

In the series 29 Rh-negative newborn infants were born. Of the group of Rh-positive children, exchange transfusion was not performed in 39 infants: eight infants were so severely affected that they died before any treatment could be started. Three infants developed mild neonatal anaemia, requiring only simple transfusions, and 28 infants showed no signs of disease. Forty-six newborn infants were treated by exchange transfusion. There were 41 survivors and five infants died, the mortality being 12·5%.

All surviving infants were followed during their stay in hospital and subsequently either by direct examination or by letter at longer intervals. One infant developed hydrocephalus with motor and mental retardation, but the relationship to haemolytic disease of the newborn is doubtful. The other cases showed neither features of kernikterus in the neonatal period nor signs of permanent damage to the central nervous system later. These favourable results are in rather sharp contrast to statements of other workers and can be explained by two facts.

(1) In our series, premature induction of delivery was almost entirely abandoned, only one infant being below 2,500 g. birth weight. (2) The development of deep jaundice was prevented by exchange transfusions repeated if necessary.

Another point of interest is the unusually high incidence of Rh-positive children without signs of haemolytic disease of the newborn. It is probable that this finding is due partly to the fact that the more reliable clinical assessment of individual cases has allowed us to be conservative with some infants that otherwise would be treated more actively.

This series of 114 infants is not entirely representa-

tive of our whole material seen during the quoted period. Cases not adequately controlled, i.e., infants born in other obstetrical centres and transferred later to our hospital or those from whom samples of cord blood were not obtained, were excluded from the present series. The total number of exchange transfusions carried out up to May, 1954, was 103 with 13 deaths.

Infants of isoimmunized women can be divided into four groups, approximately separated by the limits of normal values of haemoglobin and bilirubin as shown in Fig. 1.

(1) The haemoglobin concentration is normal or mildly decreased, and the bilirubin level does not exceed 3 mg./100 ml. All Rh-negative infants belong to this group, and in addition a certain number of Rh-positive ones without signs of haemolytic disturbance, though the Coombs test is often positive. At the borderline of haemoglobin values cases occur with a mildly increased rate of red cell destruction without deep jaundice, thus forming the picture of haemolytic anaemia. In infants with a negative Coombs test, the antibodies probably did not pass the placental barrier and the presence of haemolytic disease of the newborn is thus excluded.

(2) The haemoglobin concentration is the same as in Group I, but the bilirubin level is increased. Apparently disintegration of red cells is abnormally rapid, but foetal anaemia has not yet reached a significant degree, either because haemolysis has not been of long duration or because of sufficient compensation by increased blood production. The prognosis is good for the tissues are not damaged by previous anaemia, but the infant is threatened by severe hyperbilirubinaemia and exchange transfusion is necessary.

(3) The haemoglobin concentration is low (below 12 g./100 ml.), the bilirubin concentration increased—typical haemolytic disease with more or less advanced anaemia, the degree of which indicates the prognosis for the infant. Immediate radical treatment is necessary. Exchange transfusion, in severe cases carried out with special caution, is the best therapy.

(4) The haemoglobin is lowered, the bilirubin concentration within normal limits. As shown in the diagram, such cases are rare in practice and mean theoretically foetal anaemia of non-haemolytic origin. Wiener (1948) described such anaemias from latent bleeding in complicated pregnancies, for example, placenta praevia. Simple transfusion is the only treatment required.

It is interesting that the most severe cases presenting as hydrops foetalis exhibit, besides an extremely
low haemoglobin level, a low concentration of cord bilirubin. It is difficult to say whether the cause of this phenomenon is exhaustion of haemoglobin stores, failure of bilirubin-producing tissues or perhaps advanced changes in distribution of bodily fluids.

The great variability of haemolytic disease of the newborn is clearly shown by this grouping. There is a wide and gradual transition from the infants of Group 1, in whom the presence of the haemolytic process is indicated only by laboratory proof of passive immunization of the foetus, to the total failure of bodily defences in the hydropic foetus of Group 4.

Discussion

The fact seems to be well established that the
foetus of an isoimmunized woman is threatened by two different pathological conditions.

Severe haemolytic anaemia is the usual mechanism of death in utero. A small number of severely anaemic infants are born still alive but die within 24 hours of birth. In cord blood an extremely low haemoglobin level is found, usually below 6g./100 ml., and a fall to the level of 4 g./100 ml. means a hopeless outlook. Congestive heart failure is probably the immediate cause of death, as indicated by the raised venous pressure in the umbilical vein. There is little hope of saving these children, but occasionally a seriously affected infant can survive.

A.V., aged 24 years, a three-gravida, was group A Rh-negative, with Rh-antibodies in albumin at a titre of 1 in 32+. Her first child was normal, the second child died on the fifth day of icterus gravis. On March 5, 1953, she was delivered of a girl (birth weight 3,000 g.). The infant’s blood group was A Rh-positive. The Coombs test was +++. The baby’s general condition was very poor; she was pale, subicteric, with oedema of the face and legs and numerous petechiae of the skin. In the cord blood haemoglobin was 4-7 g./100 ml., bilirubin 6-3 mg./100 ml., and plasma proteins 3-9 g./100 ml.

The first exchange transfusion was given nine hours after birth when 300 ml. of blood was replaced. The second exchange transfusion was given 33 hours after birth and 400 ml. blood was replaced, a total exchange of 80%. The general condition remained rather poor for three weeks with loss of 21% weight and rather deep jaundice. Then her condition slowly ameliorated; the serum proteins rose to 4-9 g./100 ml. The further course was uneventful. During frequent follow-up until the present time the child appears to be mentally and physically entirely normal.

The other mechanism of death may be designated endogenous intoxication and means the failure of vitally important functions due to the toxic effects of the products of red cell destruction. This toxic stage threatens newborn infants who have escaped death from haemolytic anaemia and takes place in the period of severe hyperbilirubinaemia, i.e., within two to five days of birth. The newborn child is apparently inundated by bilirubin, the end-product of haemoglobin disintegration; there is no proof that the other products of haemolysis, potassium or porphyrins, collaborate in causing the failure of the infant’s organism.

The immediate cause of death is damage to the regulating and coordinating function of the central nervous system (failure of medullary centres) and its morphological expression is biliary staining of brain tissues. The genesis of kernicterus is not yet entirely settled and some workers still believe that bile staining of the basal ganglia is secondary to injury of the nerve cells by some other factor, i.e., by anoxia or direct activity of Rh-antibodies. Recently, however, evidence has slowly been accumulated that kernicterus is really the sequel of severe hyperbilirubinaemia, the physiological immaturity of the neonatal period being the other necessary condition of its development. This opinion is supported by two groups of observations.

The development of kernicterus is not specifically confined to the presence of haemolytic disease. The non-specific character of kernicterus was demonstrated by Zuelzer and Mudgett (1950), who found it at necropsy in a group of infants without any clinical and serological features of haemolytic disease of the newborn. As the cause of death, a heterogeneous group of pathological conditions was found, the most striking finding being prematurity in 70% of cases. Similarly Aimn, Corner and Tovey (1950) showed a rather high incidence of kernicterus in premature infants in whom the presence of haemolytic disease of the newborn could be excluded and this observation has been confirmed by many authors. Kernicterus has also been found in a group of children suffering from chronic, non-haemolytic jaundice, probably on the basis of congenital insufficiency of the liver to excrete bilirubin (Crigler and Najjar, 1952). Although these observations are sometimes interpreted by their authors in a controversial way, at least they can exclude the assumption of the directly injurious effect of Rh-antibodies as the chief cause of kernicterus.

Even more important is the fact that the development of kernicterus is closely related to the severity of post-natal bilirubinaemia. The common observation that the kernicterus occurs always in deeply jaundiced infants has been recently confirmed more precisely. Hsia, Allen, Diamond and Gellis (1952) showed by estimation of the post-natal curve of bilirubin that kernicterus is not likely to develop when the bilirubin concentration does not exceed 20 mg./100 ml., but its incidence rises sharply with increasing bilirubin, reaching 50% in cases above 30 mg./100 ml. Likewise, Mollison and Cutbush indicate 18 mg./100 ml. as the limit of maximum bilirubin concentration within which infants are not threatened by kernicterus. This quantitative connexion strongly supports the supposition that the hyperbilirubinaemia plays the primary part in the genesis of kernicterus.

There is some controversy about the part anaemia plays in the development of kernicterus. Diamond suggested that the incidence of kernicterus is independent of the degree of anaemia. On the other hand, Armitage and Mollison (1953) found a
significantly greater incidence of kernicterus in infants with low cord haemoglobin concentrations. However, anaemic infants clearly show a tendency to have a higher concentration of cord bilirubin. In our series, the relationship of the mean bilirubin values to the cord haemoglobin concentration was as follows:

<table>
<thead>
<tr>
<th>Haemoglobin Concentration (g.\textsuperscript{+})</th>
<th>Mean Bilirubin Concentration (mg.\textsuperscript{+})</th>
<th>Difference (mg.\textsuperscript{+})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 15</td>
<td>2.35</td>
<td>1.28±0.38</td>
</tr>
<tr>
<td>10-15</td>
<td>3.62</td>
<td>1.65±0.43</td>
</tr>
<tr>
<td>Below 10</td>
<td>5.24</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
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It is apparently possible to explain the relationship of anaemia to the genesis of kernicterus by its association with hyperbilirubinaemia. Nevertheless, the possibility cannot be excluded that the development of kernicterus is supported by the non-specific influence of any kind of anoxia (anaemic, anoxic, by shock), i.e., by increasing the penetrability of cerebral vessels and nerve tissues to bilirubin. These facts show that the assessment of post-natal hyperbilirubinaemia is essential for a correct decision as to therapy after birth. Ylppö, Davidson, and other workers found the relationship between the concentration of foetal bilirubin and the subsequent intensity of bilirubinaemia of the newborn: the higher the concentration in the cord blood, the higher usually is the maximum of the serum bilirubin curve within the first days after birth. Although more recent papers (Findlay, Higgins and Stanier, 1947; Hsia \textit{et al.}, 1953) show a greater variability, it is generally agreed that the cord blood bilirubin concentration almost never exceeds the level of 3 mg./100 ml. and its subsequent rise does not reach dangerous heights in normal, full-term, newborn infants. The conclusion is justified and confirmed by experience that a cord bilirubin concentration above 3 mg./100 ml. in newborn infants with serological findings compatible with haemolytic disease of the newborn indicates subsequent high bilirubinaemia and the danger of kernicterus.

Obviously, a certain number of infants with a cord bilirubin concentration just above 3 mg./100 ml. would not develop kernicterus even without any treatment, but one cannot differentiate these cases. The quantitative conditions of formation and excretion of the bilirubin in the foetal and neonatal period are poorly understood and the real height of the bilirubin curve after birth is only roughly predicted by the cord bilirubin level. Moreover, the fate of an affected infant is to a great extent determined by its individual susceptibility to kernicterus, which is highly variable and unpredictable.

We feel that an adequate margin of safety is given by setting 3 mg./100 ml. as the limit of cord bilirubin concentration for introducing therapy to prevent abnormal increase in bilirubinaemia. In full-term infants this assumption has been fully confirmed by our experience of the last four years, although values below 3 mg./100 ml. have occasionally been seen in the cord blood of erythroblastotic\textsuperscript{*} infants by other workers (Hsia, Allen, Gellis and Diamond, 1952).

In premature infants the estimation of suitable therapy must be made more cautiously. As recently shown by Hsia \textit{et al.} (1953), the post-natal rise of the bilirubin curve is higher and longer in premature infants in physiological conditions, although the foetal bilirubin is not elevated and may even be decreased (our findings). There is no doubt that in premature infants with a tendency to abnormal red cell destruction bilirubinaemia can reach dangerous heights even when the cord bilirubin concentrations do not exceed normal limits.

It is our rule to perform exchange transfusion in newborn infants of isoimmunized mothers (1) when the haemoglobin in the cord blood is below 12 g./100 ml., in which cases the bilirubin level is almost invariably increased; (2) when the haemoglobin is above 12 g./100 ml. and the cord bilirubin concentration exceeds the limit of 3 mg./100 ml.; (3) in premature infants a more individual and cautious decision is necessary. It seems reasonable to carry out exchange transfusion in every premature infant with a positive Coombs reaction.

As shown by Fig. 1, the common factor of all cases of haemolytic disease of the newborn requiring exchange transfusion is the high concentration of bilirubin in the cord blood. Many workers are satisfied by the estimation of cord bilirubin alone as the index of the necessity for exchange transfusion. This is of some advantage since the bilirubin level can be estimated subsequently in coagulated blood when samples of fluid blood for haemoglobin estimation are not obtained. The prognostic value of the haemoglobin concentration is, of course, not diminished.

We consider the combined estimation of the haemoglobin and bilirubin concentration in the cord blood the most reliable guide in the treatment of haemolytic disease of the newborn and we use the other tests only as auxiliary methods, i.e., in poorly followed cases.

**Summary**

Common methods of assessing the severity of haemolytic disease of the newborn, before and after

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\* No data are given, however, on criteria of diagnosis and severity of haemolytic disease of the newborn in these children.
ASSESSMENT OF HAEMOLYTIC DISEASE OF THE NEWBORN

Some problems of the pathogenesis of icterus gravis and kernicterus are discussed.

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