REFRESHER COURSE FOR GENERAL PRACTITIONERS

HAEMOLYTIC DISEASE OF THE NEWBORN

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Few have the opportunity of keeping abreast with the advancing knowledge about haemolytic disease of the newborn. Yet in considering the disease this knowledge must be constantly applied by medical practitioners. It seems reasonable, therefore, that the subject should be reviewed from time to time in a manner which may help the family doctor.

The severe forms of this disease have long been recognized by their clinical patterns as: (1) *Hydrops foetalis*—the oedematous stillborn infant; (2) *icterus gravis neonatorum*—the baby deeply jaundiced within a few hours; and (3) *congenital anaemia*—the baby developing intense pallor within the first two or three weeks of life. These were sometimes collectively known as "erythroblastosis foetalis." The cause remained a mystery until 1940, when Landsteiner and Wiener discovered a new blood-group substance—the Rhesus factor. This substance is present in the red cells of six out of every seven people, and these are therefore said to be Rh-positive, while those lacking the substance are Rh-negative. Should Rh-positive cells enter an Rh-negative person, as can occur when an Rh-positive foetus exists in an Rh-negative mother, then that person may react by producing antibodies able to destroy any Rh-positive cells. These antibodies, crossing the placenta, destroy the foetus's red cells. Since the clinical features—anaemia, jaundice, and oedema—found in many affected babies are mainly due to this haemolysis, the condition is best described as "haemolytic disease of the newborn."

As haemolytic disease affects only one baby in every 200 born, a busy practitioner is likely to meet a case in his own practice only every three to four years, but when he does his management may mean the difference between life and death to the affected infant. Moreover, the subject has been widely presented in the lay press, and, as one in eight marriages will be between an Rh-negative woman and an Rh-positive man, the family doctor is likely to be consulted frequently.

Nomenclature and Diagnostic Tests

By testing the blood it is possible to divide the population into two groups—those whose cells contain Rh substance being Rh-positive, while those lacking this substance are Rh-negative. The Rh group can be further divided into many subgroups. There are about a dozen Rh substances, all antigenic, but only one, D (big D), is of great clinical importance. Therefore as a routine people are tested only against anti-D serum, and confusion is avoided if D-positive or D-negative are used synonymously with Rh-positive or Rh-negative respectively. Throughout this article only the terms "Rh-positive" and "Rh-negative" will be employed, as they are already established in common usage. In order to avoid any misunderstanding many laboratories report results as Rh(D)-positive or Rh(D)-negative, or, alternatively, state the specific type of grouping serum against which the cells have been tested.

A person inherits his Rh group from both parents, so that if the Rh-positive factor is inherited from each he will be *homozygous Rh-positive*. If the Rh-positive factor is inherited from one and Rh-negative from the other, then he will be *heterozygous Rh-positive*. Children of an Rh-negative mother and a homozygous Rh-positive father must themselves be Rh-positive, while those with a heterozygous Rh-positive father have an equal chance of being Rh-positive or Rh-negative, depending on which factor is transmitted. Similarly an Rh-negative father can only hand on to his children the Rh-negative factor.

The *Coombs test*, best carried out on the infant's cord blood, is used to show whether antibodies have, in fact, crossed the placenta and coated the infant's red cells. Any newborn infant with a positive Coombs test, whether with or without clinical symptoms, must be considered to have haemolytic disease. A negative result excludes the disease. The test often but not necessarily remains positive for the first three to four weeks of life.

Errors, clerical and technical, do occur with all laboratory tests: therefore clinical evidence of disease should always be regarded, and if this is in conflict with such tests they should be repeated. Last year a doctor, when called to see a baby aged 10 days with severe pallor, found that the mother's blood-group card stated that she was Group O and Rh(D)-positive. This caused him to discard the diagnosis of haemolytic disease until the fourteenth day, when the baby was so ill that it died. But the laboratory test was at fault and later tests showed that she was actually Rh-negative.

Aetiology

The stage is set for the disease whenever an Rh-negative mother carries an Rh-positive foetus; a combination of circumstances occurring in one of every ten pregnancies. The disease will not occur in the infant unless Rh antibodies develop in the mother. Such immunization of the mother can occur if she ever receives Rh-positive cells, either by transfusion or intramuscular injection at any time in her life, or from her own foetus during pregnancy. The risks, however, are not equal. The risk of immunization by pregnancy is one in twenty, while transfusion carries a fifty-fifty risk. Thus it is imperative at all times that the transfusion of Rh-negative women and girls must be with Rh-negative blood. If an Rh-negative woman or girl has been immunized by intramuscular or intravenous injection of Rh-positive blood, the first infant, if Rh-positive, may be affected. If immunization occurs through pregnancy, the first infant is usually spared, but the likelihood of disease increases with each succeeding infant.

With this range of possibilities the disease must be kept in mind whenever pregnancy occurs in an Rh-negative woman, and must be expected if Rh antibodies are found in her serum. Once immunization has occurred it is permanent, and every subsequent foetus is at risk.

Common Clinical Patterns

Babies affected with haemolytic disease may show differing pictures, varying from the baby without clinical evidence of disease to the hydropic stillborn foetus. Cases may fall anywhere between these extremes, but in general we recognize four fairly distinct types.

1. Subclinical Variety

This is the Coombs-positive baby in whom the diagnosis cannot be made on clinical grounds, and who requires no active treatment. Such cases are nearly always detected because antibodies have been found in the mother's serum before delivery and therefore the Coombs test has been done on the baby's cord blood at birth. Some babies in this group may have transient jaundice indistinguishable from physiological jaundice of the newborn, and anaemia, if present, is minimal, of short duration, and does not require active treatment.

2. Anaemic Variety

This is the baby in whom pallor is the striking feature. Anaemia usually becomes evident towards the end of the first week and increases thereafter. If not recognized early, by careful attention to the colour of the mucous membranes, pallor may only be noticed as late as three to four weeks, when the haemoglobin level can be as low as 20% and the baby's life is in danger. Jaundice often occurs in these infants, but, although frequently of earlier onset and perhaps of greater depth than the physiological variety, it is in no way diagnostic, nor is it essential for the diagnosis. Pallor in a baby may be easily overlooked unless the eye be trained to recognize it. Moreover, if jaundice is present, pallor may be obscured and only become evident when jaundice fades. One evening a doctor telephoned to say that an 8-day-old baby had "rhesus disease." In answer to questioning we learnt that the baby seemed lively and took its feeds well. The baby, he said, "was quite a deep orange colour a few days ago, but is much better now—it is only a pale lemon colour." We should have been alarmed rather than reassured by that description, for that baby while being brought for examination the next morning died from anaemia in its father's arms in the hospital lift.

Even now there is a considerable mortality in this anaemic type of disease which could by careful supervision of each baby be reduced to less than 1%. In the first six weeks, in addition to assessing the general condition of the baby and observing the colour of mucous membranes, haemoglobin estimations should be made every two to three days (and, if low, even more frequently). No elaborate method is needed, and the "Tallqvist" method* is accurate enough at levels below 50%. With the aid of this simple test, no child need die solely because anaemia has not been recognized.

Recently we have seen two babies who owe their lives to such careful observation. The first was a baby in a small maternity hospital who at the age of 5 days was noticed to be pale. As treatment entailed a night journey of 60 miles (96.5 km.) it was suggested that a haemoglobin estimation be made. This was done by a complex method and the result was 65%, but the matron insisted that the baby looked much paler than this and that she proposed to bring it to hospital nevertheless. On arrival three hours later the haemoglobin was 35%; the baby was transfused and recovered. The second was a baby, said to be Coombs-

negative and therefore unaffected, discharged from a maternity hospital. In the face of this, the family doctor recognized the occurrence of abnormal pallor at four weeks and sent the baby back to hospital. It was found that the report of a negative Coombs test had been sent in error, and this baby also survived.

3. Deeply Jaundiced Variety

This is the baby with early rapidly deepening jaundice and early progressive anaemia. Many babies in this group have enlarged liver and spleen. Some have small round clearly defined bruises of the skin, especially on the face, but sometimes also on the trunk and limbs. The jaundice may obscure pallor, which is difficult enough to recognize in a newborn baby in any case. Yet the degree of anaemia at birth is often closely related to the outlook for the baby; hence in hospital it is customary to do a haemoglobin estimation on the baby's cord blood. A level of less than 50% invariably means severe disease with a very high mortality rate, whereas levels of more than 100% are frequently associated with mild disease having a low mortality rate.

The mortality in this, the deeply jaundiced variety of haemolytic disease, is high, death usually being due to: (a) heart failure on the first day in babies grossly anaemic at birth; (b) brain damage during the first week, usually in deeply jaundiced babies; or (c) haemorrhages into internal organs.

3a. Brain Damage (Kernicterus)

This complication is almost completely confined to deeply jaundiced babies and is therefore best considered at this point. Of all liveborn babies with this illness, one in twelve suffers brain damage, the diagnosis usually being evident in the first week of life.

Neurological diagnosis in the newborn is notoriously difficult, but one should consider the possibility of kernicterus if a deeply jaundiced baby with haemolytic disease suddenly, at about the third or fourth day, develops head retraction. Other features often develop, particularly extensor spasms of the arms and legs with clenching of the fists. A shrill cry, vomiting, and fits complete the picture. Once kernicterus has occurred, treatment is of no avail and death from respiratory failure usually follows in a matter of days. The few that survive have permanent brain involvement, which is discussed later.

It is not uncommon for any jaundiced baby to be drowsy and to take feeds badly. This in itself does not denote kernicterus, but if neck stiffness develops it is important to obtain specialist opinion. To distinguish kernicterus from cerebral birth injury and other cerebral disease will require expert examination by a doctor experienced in the care of the newborn child.

4. Stillborn Variety

The most severe form of haemolytic disease kills the foetus. The stillbirth due to haemolytic disease often presents a peculiar appearance. It is grossly oedematous, with protruding tongue, waterlogged tissues, and free fluid in all the body cavities. Pallor is extreme and the liver and spleen are greatly enlarged. Very occasionally a grossly oedematous baby is liveborn but dies in a matter of minutes. We must not oversimplify the position, and it must be realized that oedematous stillbirths may be caused by diseases other than haemolytic disease. Nor are all haemolytic disease stillbirths oedematous; many are indistinguishable

*See *British Medical Journal*, 1951, 1, 1093.

superficially from stillbirth due to other causes. Of course a foetus with haemolytic disease may be stillborn owing to causes other than the disease itself.

Essentials of Treatment

The first essential is early diagnosis. All cases should be anticipated by blood-grouping tests carried out before delivery. The routine antenatal blood-grouping tests are detailed later, but if antibodies are detected haemolytic disease is to be expected.

Every mother whose serum contained antibodies should be delivered in a hospital specially prepared to treat haemolytic disease of the newborn, which is a difficult technical procedure often requiring early exchange transfusion. Furthermore, as there is a high incidence of post-partum haemorrhage in the mothers of these babies, it is desirable that they, too, should have facilities for early treatment with Rh-negative blood, if needed.

Once antibodies have developed they cannot be nullified, nor, within the limitations of our present knowledge, can the foetus be protected from their action.

Premature Induction of Labour.—There is evidence that premature induction does not improve the baby's chance of survival, and therefore we ourselves have not used this form of treatment. Moreover, nothing could be more tragic than that an Rh-negative baby, and therefore an unaffected one, should be delivered before term and die because of prematurity. There may be a case for premature induction in families in which there is a previous history of stillbirth due to *haemolytic disease*, but only if the father is homozygous Rh-positive, meaning that all his children must of necessity be Rh-positive and therefore affected.

Blood Transfusion.—Few would question the value of simple transfusion for the relief of anaemia during the course of the illness. Recently, early exchange transfusion in babies with severe disease has held out some hope of a reduction in mortality, and also in the prevention of brain damage. These are hospital procedures, and if the baby is to be given the best chance it must be delivered in hospital.

Breast-feeding.—It has been suggested that breast-feeding may be harmful in this disease, by transferring additional antibodies from the mother to the baby. We encourage breast-feeding in all cases of this disease, and prolonged haemolysis due to this cause is extremely rare.

Contribution of the Family Doctor

The family doctor shares with the midwife and the staffs of antenatal clinics the responsibility of antenatal diagnosis of this disease. He must sometimes also consider the diagnosis in families in which full blood-group studies have not been made and in which the first indication of trouble may be the appearance of suggestive symptoms in the baby.

Clinical evidence of haemolytic disease should never be disregarded, and, when there is doubt, further opinion should be obtained even if the parents' blood groups are known and are not the classical "set up" of Rh-negative mother and Rh-positive father.

As babies with this illness must be kept under observation until the age of 6 weeks, the hospital will probably wish the family doctor to share in this. Hence it is desirable that he should be familiar with the possible courses of this illness. He should also seek to protect his patients

from the advice so many ill-informed people seem anxious to give, and should make it his responsibility to make sure that they receive only the best advice available.

The responsibility of the family doctor is considered under the following headings: (a) to detect families in which haemolytic disease will probably occur; (b) to diagnose the disease in families in which blood-grouping tests have not been carried out; and (c) to advise the Rh-negative person.

(a) To Detect Families in which Haemolytic Disease will Probably Occur

This is done by the following routine serological tests on every expectant mother before delivery (see Diagram).

1. *Determine the Rh Group of the Mother at her First Attendance.*—If Rh-positive (six out of seven women) there is no further need for tests in the absence of clinical disease in the infant. If Rh-negative the mother may become immunized by pregnancy if her husband is Rh-positive, therefore:

2. *Determine the Rh Group of the Husband.*—If Rh-negative there is no need for further tests in the absence of clinical disease in the infant, and the mother can be told that there is no risk. If Rh-positive the mother should be told that it is a twenty-to-one chance against anything going wrong, but that tests on her blood must be made between the thirty-second and the thirty-sixth week of each pregnancy. If the father's blood is not available for grouping he should be assumed to be Rh-positive.

3. *Test the Mother's Serum for Antibodies Between the Thirty-second and Thirty-sixth Week of Every Pregnancy.*—If antibodies are not present no disease of the infant should be anticipated and the pregnancy should be treated as normal. However, a specimen of *cord blood* from the baby at birth should be obtained for the Coombs test and Rh grouping, as these will detect haemolytic disease even if antibodies were not detected because of technical error or failure to collect the specimen. If the baby is Rh-negative and the father is known to be Rh-positive, it will establish that he is heterozygous. If antibodies are present the baby will, if Rh-positive, suffer from some form of haemolytic disease, and arrangements should be made for its delivery in hospital. Every now and again, under these circumstances, the baby will be Rh-negative, the same as the mother, and therefore unaffected. One cannot predict accurately the group of the baby before birth, but some indication can be obtained by genotyping the father.

4. *Determine the Genotype of the Father.*—If homozygous, the doctor is in a position to tell the parents that the baby is certain to have some form of haemolytic disease; if heterozygous, that there is a 50% chance that it will be Rh-negative and therefore normal. Although of limited value when a woman is pregnant, the knowledge of the genotype will often enable parents to face the question of further children more intelligently.

The previous history of one of our patients may be of interest. Her first pregnancy ended in abortion, and blood transfusion was necessary to save her life. She was given 4 pints (2.3 litres) of blood, the Rh group of which was unknown. The next pregnancy resulted in a baby who became severely anaemic during the second week of life,

and who was admitted to hospital but died of anaemia. The next two pregnancies resulted in stillborn hydropic foetuses. At this stage her husband was genotyped and found to be heterozygous Rh-positive. This gave her a fifty-fifty chance of a normal baby, and this year she was delivered of a healthy Rh-negative daughter.

5. *Cord Blood must be Collected from the Babies of all Mothers with Antibodies.*—The specimen is used for Rh grouping and the Coombs test. If Coombs-positive the diagnosis of haemolytic disease is established, if Coombs-negative the diagnosis is excluded and the baby is presumably Rh-negative.

Antenatal Blood-grouping Tests

To summarize: By means of blood-grouping tests it is now possible to determine which mothers are at risk, to anticipate disease in nearly all cases, and to establish the diagnosis within a few minutes of birth. Tests for the strength of antibodies in the mother's blood are not of much value in predicting the form or severity of the disease in the baby, and are not required. The determination of the father's genotype will often help parents to face the future more confidently, and should be suggested in any family in which the mother has antibodies.

(b) To Diagnose the Disease in Families in which Blood-grouping Tests have Not Been Carried Out

A practitioner called to see a baby who is jaundiced or pale in the first few weeks after birth should always consider the possibility of haemolytic disease. The clinical picture may be so striking that the diagnosis is certain, but in other cases it may be impossible to make a definite diagnosis without recourse to serological tests.

If a baby is heralded by yellow liquor, is pale at birth, and yellow within eight hours, with enlargement of liver and spleen, the diagnosis is sure and the disease is severe. In addition, should there be small round well-defined bruises of the face, trunk, and legs, or frank haemorrhage from any mucous membrane, or if oedema is present, treatment is urgent.

Jaundice in the first 24 hours (best seen over the abdominal wall with the skin stretched) is due to haemolytic disease until it is proved otherwise. Proof of

diagnosis can only readily be obtained by serological investigation, and this should always be carried out. While of such immense diagnostic importance, early jaundice does not invariably mean severe disease. A history of clinical disease suggesting haemolytic disease of the newborn in previous children may be helpful in some cases, but is by no means always present.

Anaemia occurring in the neonatal period is most likely to be due to haemolytic disease. Oedema, if severe, is a sign of impending death. Haemorrhage, apart from petechiae on the trunk or face, gives cause for alarm. Anaemia is of prognostic value, while jaundice is that which focuses attention.

(c) To Advise the Rh-negative Person

To answer many of the questions asked by Rh-negative women is often difficult because no single test or combination of tests gives a precise indication of the outlook. However, by the simple expedient of grouping the husband's blood, one in seven will be found to have Rh-negative husbands and can therefore be told that there is virtually no risk. Those with Rh-positive husbands can be told that there is only a one-in-twenty chance of any trouble. If antibodies are not present at 32 to 36 weeks the mother can be told that the baby will not have haemolytic disease. If, however, antibodies are detected the mother must be told that the child may have haemolytic disease, and that she should be delivered in a hospital prepared to treat this disease. Serological tests, unfortunately, are of little value in predicting the form or severity that the disease is likely to take in the baby, and we have found the previous history of only limited value.

The first baby is unlikely to have haemolytic disease unless the mother has been exposed to the risk of immunization by previous blood transfusion, but all are familiar with the difficulty of being certain that any pregnancy is indeed the first. In general, the first affected baby is but mildly affected and recovers completely. Subsequent babies are likely to have increasing degrees of severity, and, in particular, the occurrence of a stillbirth due to haemolytic disease of the newborn will increase the chance of subsequent pregnancies ending in this way. The sequence of progressive severity is happily not invariable, so that a mildly affected baby may follow one severely affected, dying with brain damage, or even stillborn. The converse is also true—namely, that the first affected baby may be severely affected or even stillborn. Some families tend to produce identical disease in all children, as in one family in which three affected babies have survived after transfusion for relief of anaemia during the second week of life.

The probable form that haemolytic disease took in the earlier children can be assessed only by questioning on such points as stillbirth, jaundice, anaemia, etc. If previous children have died, then information concerning age and mode of death may be helpful in the assessment.

Finally, our evidence suggests that immunization produced by transfusion is of the same significance as that caused by pregnancy.

Outlook for Affected Infants

I have had the opportunity of studying 600 cases of this disease in recent years. Approximately 15% were

stillborn. Of those born alive, approximately 15% died. Included in these there are some deaths that I believe could have been avoided.

Of all liveborn babies with this illness, one in twelve suffers brain damage, the diagnosis usually being evident in the first week of life. Most of these children die, if not in the first week, then frequently in the first month. A few children with evidence of brain involvement do survive, and such damage may lead to deafness, speech defect, mental defect, or motor disturbance of choreo-athetoid type. Survival is exceptional, however. In fact, 99% of our surviving cases show no gross abnormality. Occasionally teeth of the first dentition may be green, but are otherwise healthy and greatly prized by patient and dentist alike. The permanent teeth are never affected. I know of no other condition definitely attributable to haemolytic disease.

Summary

Haemolytic disease of the newborn may occur whenever an Rh-negative woman carries an Rh-positive foetus.

The disease can be anticipated in almost every case by the family doctor knowing the Rh grouping of the parents in his practice, and seeing that the pregnant Rh-negative mother is tested for antibodies without fail between the thirty-second and thirty-sixth weeks of pregnancy.

If antibodies are present clinical disease can be expected in the infant, and although the severity may vary it is best for such mothers to be delivered in hospitals prepared to treat this illness.

This means that transfusion with Rh-negative blood can be given by the direct or exchange methods without delay; the infant should be carefully watched during the dangerous first week of life.

Should the birth take place at home, a specimen of cord blood should always be taken.

Jaundice in the first 24 hours is due to haemolytic disease until proved otherwise.

After this, when the infant returns home, or in children born at home, the doctor must be on the look-out for delayed anaemia until the sixth week.

In view of the dangerous sensitivity which follows the transfusion of Rh-negative women with Rh-positive blood, all women known to be Rh-negative or women whose Rh group is unknown should be transfused only with Rh-negative blood.

Although immunization through pregnancy cannot be avoided, and immunization, once present, persists for life, a knowledge of the father's complete Rh type and the previous obstetric history will help the family doctor to give some advice about future pregnancies.

If the results of laboratory tests conflict with the clinical picture, such tests should be repeated.

Finally, I would counsel doctors to be careful not to cause unnecessary alarm. To give a gloomy prognosis to all Rh-negative women is a heedless procedure. For, although tragedies occur all too often to women who greatly desire a family, they are outweighed by the unexpected successes, many of which are not yet to be explained by the modern understanding of this disease.

In *Nature* (October 13, p. 651) Dr. R. W. G. Wyckoff publishes electron microscope photographs showing influenza virus particles apparently growing out of infected cells of the chick embryo. That is to say, diseased cells are seen in section to have many small cytoplasmic protrusions from their borders, and these protrusions break off as spheres of the same size and shape as influenza virus particles. Further, these phenomena are not observed in healthy tissues, but only after infection with influenza or Newcastle disease. The work is important for the light it throws on the nature of viruses.

DAME HILDA LLOYD: PRESENTATION PORTRAIT

The 34th annual general meeting of the Medical Women's Federation concluded on November 2 with a presentation of her portrait to Dame Hilda Lloyd. The portrait, which is the work of Mr. Anthony Devas, depicts her in her robes as president of the Royal College of Obstetricians and Gynaecologists.

The President of the Federation, Dr. Doris Odum, in making the presentation before a large audience of women

doctors at B.M.A. House, London, spoke of Dame Hilda Lloyd's eminence in her profession and of the warm affection in which she was held by all her colleagues. She had had an outstanding career in her native city of Birmingham as consultant at the Women's and Maternity Hospitals and as professor of gynaecology and obstetrics at the United Birmingham Hospitals and the University. Women doctors had great pride in the high office to which she had attained in the Royal College—the first woman to hold such an office in any of the Royal Colleges.

Dame Hilda Lloyd said that this occasion gave her the greatest pleasure she had known in her professional life. She had qualified the year before the Federation was established, and she became a founder member under the stimulus of Dr. Mary Sturge, of Birmingham, who followed Dr. Jane Walker as second president. She recalled the names of some of those associated with the earlier days of the Federation—Lady Barrett, Florence Ivens, Christine Murrell, Violet Kelynack, Catherine Chisholm, Clara Stewart, Louisa Martindale, among others. It was sometimes said that the Federation was superfluous because the British Medical Association treated men and women doctors on equal terms. Nevertheless, the Federation was the body to which the Association turned for the views of medical women. The days were not long past when equal opportunities for medical women could not be taken for granted but had