THE PRACTICAL APPLICATION OF THE RHESUS BLOOD FACTOR TO THE ART AND PRACTICE OF OBSTETRICS

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Introduction

The subject has been chosen for three reasons. First, because in the space of just a few years the rhesus blood factor has assumed world-wide interest and import, and has already come to merit a most important place in the realm of obstetrics. Secondly, its practical significance does not yet seem to be fully appreciated or realized, and thirdly, study has proved this subject to be much more complicated than was at first thought.

A considerable amount of knowledge has been accumulated in these last few years, but there is still much more to be found out, both practically, and on the research side as well. The picture is incomplete and its completion depends on the close interdigitation of the practical with the research side, and the seeing that no available material is missed.

The purpose of this article is not to diverge into research problems or those relating to blood transfusion, but to indicate the particular influence that this recent research has on practical obstetrics. It is essential, however, to include brief references to the research that has made this practical application of it not only possible, but necessary.

The Rhesus Blood Factor

The rhesus, or Rh factor, is a new blood agglutinin. In 1940, Landsteiner and Wiener injected red cells of the Rhesus monkey into rabbits and guinea pigs. This produced an immune serum, which agglutinated the red cells of 85 per cent. of American Whites, and failed to react with the other 15 per cent. Human bloods agglutinated by this serum were called Rh positive (denoted Rh or R), and

those which did not, Rh negative (denoted rh or r).

Arising from the investigation of certain haemolytic transfusion reactions, which showed them due to Rh positive blood being given to Rh negative subjects, or vice versa, it was noted that where such reactions occurred after transfusions in the puerperium, there was often an associated foetal abnormality.

The Genotypes of the Rh Factor

It is advisable, before discussing this associated foetal abnormality, to set out clearly what is meant by the genotypes of the Rh factor. In 80 per cent. of cases the Rh genotypes can be accurately recognized serologically. They represent the fundamental constitution of given individuals. The human cell possesses 24 pairs of chromosomes. At fertilization, with the union of the sperm and ovum, one chromosome of each new pair formed comes from the male side, and the other from the female side. Thus, as far as the Rh factor is concerned, the foetus derives 50 per cent. of its genotype from the father, and 50 per cent. from the mother.

Much, then, depends on whether the parents are homozygous, that is, their pairs of chromosomes are identical as regards Rh factor, or whether they are heterozygous, where the pairs of chromosomes are not identical as regards Rh.

A homozygous person is denoted Rh Rh (R.R.) on the positive side, and rh rh (r.r.) on the negative. A heterozygous person is denoted Rh rh (R.r.), that is, a combination of positive and negative. The Rh negative gene (rh) is recessive, so that a heterozygous person is always Rh positive.

It can be seen, therefore, that a homozygous Rh positive (Rh Rh) father when mated to an Rh negative (rh rh) wife, can only produce a heterozygous but yet Rh positive child. Once his wife has become sensitized to his Rh positive, his chance of producing an unaffected child is almost nil. On the other hand, a heterozygous father (Rh rh) mated to an Rh negative (rh rh) wife, has a 50 per cent. chance of producing an Rh negative and so unaffected child.

It is, however, not quite such plain sailing as this, because the various allelomorphs of the Rh gene have to be taken into account, as each may produce a different agglutinin. Also, what can be termed reverse Rh reaction can occur, that is, a homozygous Rh positive (Rh Rh) wife may be sensitized to her husband's Rh negative gene (rh rh, or Rh rh).

The writer's opinion is that the genotype is *all* important as regards the prognosis and treatment in cases where the Rh factor is involved, and that such cases can neither be intelligently nor scientifically handled, unless the genotypes of both parents and the child are known.

Examples will be given later of how it is possible to presume, in the absence of genotypes, that a new-born baby is suffering or will suffer from 'haemolytic disease of the new born,' and that its life has been saved by immediate transfusion. The genotypes in such cases will often prove that the occurrence of haemolytic disease of the new born was an impossibility, that the transfusion was quite unnecessary, and the claim to success entirely erroneous.

Relationship of the Rh Factor to Obstetrics Generally

In 1941, Levine, Burnham, Englewood, Katzin and Vogel demonstrated that many transfusion reactions in the puerperium were definitely associated with what Parsons has since termed haemolytic disease of the new born, comprised of hydrops foetalis, erythroblastosis neonatorum, icterus gravis neonatorum and haemolytic anaemia.

This work has been amply confirmed by Boorman, Dodd and Mollison, and by Taylor, Race and others, and can now be regarded as proved fact.

The condition is due to isoimmunization of the mother to an antigen present in the foetal erythroblasts, because of the fact that an Rh negative mother is carrying an Rh positive foetus. An antibody is thus formed in the mother's blood, and it crosses the placental membrane to the foetal circulation, and there destroys foetal red cells, producing the condition of intravascular haemolysis.

Javert (1937) estimated the occurrence of haemolytic disease of the new born as 1 : 400 births. Taylor (1944) estimated it at 1 : 200 births.

Obviously, therefore, haemolytic disease of the new born is a definite cause of infant mortality. It is also known that survival from it in the past, especially after the onset of kernicterus, is associated with mental deficiency.

The Rh Factor and Antenatal Care

The ideal is obviously the routine determination of the genotype of husband and wife in all cases of pregnancy. The future may bring this, but at present the laboratories of the country have neither the staff nor the materials to do it.

In the writer's own area, at all antenatal clinics, the mother's blood is tested as to whether it is Rh positive or negative. Given a negative result, the family genotypes are investigated. This is also done even if the mother is Rh positive, in any case where the previous history suggests Rh factor involvement. This is not perfect, but is a step in the right direction.

It is apparent that the previous history should be taken with even more detailed care and thought than ever. In every case of abortion for no apparent reason, stillbirth, intrauterine death of the foetus, maceration, death soon after birth, especially if associated with hydrops or icterus, premature labour, abnormality of the foetus, and mental deficiency, the family genotypes, including the affected foetus, and any living children, should be investigated.

In cases where the family genotypes indicate the possibility of Rh factor involvement, the mother's blood should be routinely examined, throughout the pregnancy, for antibody. It must be borne in mind, however, that antibody

is rarely demonstrable before the 32nd week of pregnancy. In some cases, the mother may show a certain degree of icterus near full term or in the early puerperium.

The Rh Factor and the Confinement

This must be considered under two separate headings.

(a) Cases where the Rh factor involvement can be anticipated.

(b) Cases where the Rh factor involvement has not been anticipated.

(a) *The anticipated case*

Either the previous history or the finding by routine examination of an Rh negative mother, have led to investigation of the family genotypes. If the investigation has been a routine one, the case should be kept under strict supervision and all preparations made to cope with trouble should it arise. For reasons not as yet known, isoimmunization of the mother does not occur in every case where the combination of genotypes renders it possible.

Where the previous history shows that haemolytic disease of the new born has already occurred in the family, the outcome of the case depends on the actual combination of family genotypes.

If it is a homozygous Rh positive father ($Rh_1 Rh_1$) and an Rh negative mother ($rh rh$) or vice versa, and she has already been sensitized to her husband's Rh gene, then haemolytic disease of the new born can be definitely predicted, whether or not antibody is ever demonstrated in the mother's blood.

The different allelomorphs of the Rh gene seem definitely to have a bearing on the outlook. Where, for instance, a father ($Rh_1 Rh_2$) is mated to a negative mother ($rh rh$) it seems possible for her to be sensitized to his Rh_1 and produce babies suffering from haemolytic disease of the new born, and yet in a subsequent pregnancy produce a child of genotype $Rh_2 rh$, which is unaffected.

The appearance of Rh antibody in the mother's serum, is proof positive of Rh factor involvement. The non-detection of antibody, however, by no means excludes the possibility of haemolytic disease of the new born. This means that there may be antibodies as yet unidentified, or that present techniques are inadequate.

A significant increase in the cases of demonstrable antibody can be shown by the special techniques such as those of Weiner, Race, etc., for eliciting 'incomplete antibody.'

Sometimes antibody can be detected in the mother's serum 7-10 days after the confinement, where previously all findings were negative. At other times, a child is born which rapidly dies due to kernicterus, and at no time during the pregnancy or the puerperium has it been possible to demonstrate antibody.

It has been recommended that where haemolytic disease of the new born can be predicted, that Caesarean section be performed at approximately the 38th week, followed by immediate transfusion of the child. The reason given is that kernicterus probably starts to develop some two weeks prior to full term. It is also claimed that affected babies are prone to asphyxia during their passage through the birth canal.

That kernicterus does commence to develop at, or soon after, birth, and that it progresses rapidly, is not disputed. The writer, however, cannot subscribe to an affected foetus being more prone than any other to asphyxia during birth.

It would seem, that for the present state of knowledge, the pendulum has swung too far. Before such a radical line of treatment could recommend itself to those who practise obstetrics, fuller proof will have to be given (a) that kernicterus does develop before full term, (b) that normal labour in a multipara prejudices the child's chance of survival—because labour can always be induced at the 38th week or earlier, (c) that the results obtained by Caesarean section eclipse those by induction.

The writer's experience in predictable cases is that the immediate and distant grave prognosis for the child constitute a very definite contraindication to radical methods, and that conservative lines of treatment can achieve equivalent results. If the titre of a demonstrable antibody rises towards full term, as it sometimes does, immediate induction of labour is indicated.

When, however, by whatever means the child is delivered, the following procedure should at once be carried out.

(a) Taking care not to foul with Wharton's jelly, which inhibits agglutination, two specimens of cord blood are taken, one with heparin, the other without.

(b) Specimen of mother's blood from a vein, if one has not very recently been taken.

(c) Blood films from the child.

The child's blood is examined for icterus and its genotype determined. The stained films are examined for signs of erythroblastosis. A predominance of early primary erythroblasts over normoblasts is pathognomic of haemolytic disease of the new born.

(b) *The non-anticipated case*

No investigation has been done because no suspicions had been aroused.

It is usually a second baby, the first having been quite normal except, of course, that the mother's blood had been sensitized thereby. Sometimes it is a first pregnancy, at other times two, three, or more normal babies have been born before sensitization of the mother has occurred.

The baby may die *in utero* and become macerated. It may show hydrops foetalis, where birth is usually premature at the 32nd to 34th week. The degree of hydrops is variable. Ascites may obstruct labour. The placenta is large, anaemic and friable. The child does not survive. Rh factor investigation should always be done, should the mother of a macerated foetus or of a hydrops foetalis, require transfusion. Fatalities have occurred for want of this. An Rh negative woman, during the child bearing age, should always receive Rh negative blood. Diamond has shown a higher incidence of haemolytic disease of the new born in Rh negative mothers who have previously been transfused with Rh positive blood.

The baby may look perfectly normal at birth, at full term. Jaundice, however, may appear a few hours after birth and increase very rapidly. This is icterus gravis neonatorum, as opposed to physiological jaundice, which rarely appears earlier than 48 hours after delivery. These babies may also show haemorrhages into mucous membranes under the skin, or from the umbilicus.

Very soon as the jaundice deepens the baby may develop twitchings, irritability of

the cerebral type, followed by deep drowsiness, nystagmus rigidity, local or generalized, or even convulsions. Its general condition deteriorates rapidly, and anaemia becomes obvious, despite the jaundice. This signifies kernicterus, which is characterized pathologically by a bright yellow pigmentation of the nuclear structures of the brain. Death usually occurs on the second, third, or fourth day after birth.

In congenital anaemia, the child may appear normal at birth, or look pale and anaemic. Inside two or three days, however, marked pallor and anaemia can be observed, the skin assuming an almost transparent appearance. At birth the liquor amnii and vernix caseosa often have a yellow or orange colour.

As before, the mother's blood, foetal blood and films are sent for examination as soon as the diagnosis is suspected.

Treatment of the Child Affected with Haemolytic Disease of the New Born

As soon as possible after delivery, and this the writer believes to be most important as regards success, the child is transfused with specially selected blood. This blood is the same Rh group as the mother (usually Rh negative) and has been matched against her serum. The mother's blood must never be given. The blood must be given intravenously and, if ready and waiting, can be given via the umbilical cord. The malleolar veins, or veins in the arm, however, are more suitable, as the giving of an adequate amount of blood takes considerable time. The amount of blood given is regulated by the size of the child, 200-250 ccs. being the amount aimed at for a 7 to a 7½ lb. baby.

The idea behind the transfusion is to 'damp down' the activity of the child's bone-marrow, and so curtail its production of red blood corpuscles as they are sensitive to, and destroyed by, the antibody present in the circulation. The cells of the transfused blood are not sensitized to the antibody, are destroyed more slowly, and so prevent the child dying from anaemia, and avert the onset of kernicterus, both of which may otherwise occur from intravascular haemolysis. Thus, until the antibody has, so to speak, worked itself out, the child is kept alive by the transfusion, or repeated transfusions if necessary. The degree

of anaemia which shows the rate of intravascular haemolysis, is the guide as to when and how often to transfuse. Frequent haemoglobin estimations are, therefore, necessary, and the more rapidly the percentage falls, the more frequently will transfusion be required.

Once kernicterus has developed, there is no evidence that transfusion plays any helpful part. Those children who survive kernicterus show mental backwardness or deficiency, or imbecility often associated with spasticity and frequently athetoid or choreiform movements.

At present, breast feeding is considered inadvisable even though the milk is found free from antibody. On present knowledge that is no guarantee that it might not contain some, as yet unidentified, antibody.

Prognosis—Immediate and Remote

A. Immediate

Gimson (1943) transfused 18 cases with Rh negative blood, and reported 14 'perfect' recoveries and four satisfactory.

Cappell (1944) transfused 17 cases of which 16 recovered and one, with proved kernicterus, died.

In neither of these reported series were the genotypes of the babies ascertained. Therefore, it is felt that they cannot be taken as giving any true picture of the real prognosis. It is possible, in the absence of the babies' genotypes, that transfusions were given to infants not suffering from haemolytic disease of the new born.

To obtain a comprehensive picture of the prognosis it is wise to consider the problem as follows :—

(a) A homozygous Rh positive father mated to an Rh negative wife or vice versa, where haemolytic disease of the new born has already occurred in some form in the family.

Haemolytic disease can be here predicted. It may manifest itself in several ways for example abortion, death *in utero*, stillbirth, maceration, foetal abnormality, premature labour with or without hydrops foetalis. If the child is born alive, apparently normal, there is no guarantee that one or repeated transfusions will save its life or prevent the onset of kernicterus. Recovery from kernicterus is almost synonymous with mental deficiency. Once kernicterus has appeared in a family,

subsequent children are more liable to develop it.

(b) A heterozygous father mated to an Rh negative wife.

Here, even though haemolytic disease has already occurred in the family, there is a chance of the baby attaining the same genotype as its mother, and so be unaffected.

Where antibody has been detected during the pregnancy, however, the outlook can be the same as for (a), and can be, even though no antibody has been demonstrable. The only way to find out whether the child has escaped affection, is to ascertain its genotype.

(c) A non-anticipated case of haemolytic disease whatever may be the combination of family genotypes.

Often kernicterus develops, so to speak, with the diagnosis of Rh factor involvement, and the child may die before blood investigation can be completed or treatment given. Of necessity, there is a definite delay between the onset of the disease and transfusion of the child, and so treatment may fail to save the child or prevent kernicterus. Repeated transfusions are often necessary. The outlook for such children is not good, although some survive.

(d) The anticipated case with genotype combinations as for (a) and (b), and where the child is born alive, at or near full term, and either apparently normal or showing some icterus or anaemia. If kernicterus does not develop, and if the haemoglobin percentage has been stabilized, even though much below normal, by one or more transfusions, the immediate prognosis is reasonably good. Anaemina injections, $\frac{1}{2}$ cc. daily, and ferri et ammon. cit. by mouth are of considerable benefit, cause a rise of haemoglobin percentage, and may save repetition of transfusion.

The child must be kept under strict supervision and its blood picture checked at intervals. There is no doubt that between the third and sixth month of infant life, some babies tend to relapse again to a condition of severe anaemia, which may prove fatal. The strictest supervision must not be relaxed until the child has been proved to maintain a normal blood picture.

(e) Cases where the family genotypes show that Rh factor involvement is theoretically possible, but where haemolytic disease of the

new born has not as yet occurred in the family, and where antibody has not been detected.

First babies are usually, but not always, unaffected. Second babies are often affected, especially with a homozygous combination of genotypes. However, for reasons as yet unexplained, haemolytic disease of the new born does not by any means occur in all cases where it could be expected to do so. Why some women become sensitized and others do not has still to be determined.

B. Remote prognosis

This is a matter that only time will solve. All immediately successful cases must be followed up as regards their adolescent and adult mental calibre in order to prove that what has been done has been worth while.

Heredity and the Rh Factor

The Rh positive gene is inherited as a mandelian dominant, the Rh negative gene being recessive. It is inherited quite independently from the A.B.O. groups, and there is no sex linkage.

Race and others (1944), and Levine and Weiner have shown that there are at least seven allelomorphs of the Rh gene:—Rh₁, Rh₂, Rh₀, Rh¹, Rh¹¹, rh and Rhy. These account for 28 clearly defined genotypes. 93 per cent. of the population fall into one or other of six genotypes (combinations of Rh₁, Rh₂ and rh), whilst the other 22 are distributed among the remaining 7 per cent.

Rh¹ and Rh¹¹ cells should be considered as Rh negative in the possible recipient of a transfusion, but as Rh positive in a prospective donor.

The Future

The complexities of the Rh factor seem to be multiplying as the research advances. Further changes and alterations will necessarily have to be made in the practical application as added research discoveries lead on to wider knowledge.

Analysis of 100 Cases

When a cross section is taken through 100 cases of the writer's series, a number of interesting and also significant facts are revealed.

Of 33 primiparous Rh negative mothers discovered by routine Rh factor investigation, two were sensitized to their husband's Rh positive. Antibody was demonstrated in their serums, their babies developed haemolytic disease of the new born, were transfused and survived. These two cases, therefore, appear in the number of babies transfused.

Five were married to Rh negative husbands and so the Rh factor was not involved.

Of the remaining 26, 12 were married to homozygous husbands, and 14 to heterozygous husbands. Of these latter, seven achieved Rh negative babies.

Of 19 cases thus left over, all bore live children. Six were entirely normal, but 13, although showing no clinical signs of haemolytic disease of the new born, showed marked, proved and progressive anaemia; three at birth and the others by the fourth to eighth week. All were treated with anahaemin injections and iron by mouth, and have done well.

That such a large proportion showed progressive anaemia gives ground for conjecture, but only a further pregnancy will show whether or not it meant that these mothers had been sensitized by their first conception and whether, in their second, haemolytic disease of the new born should be anticipated.

The other 67 cases were multiparae, investigated either because of their previous history or because the new-born child showed signs of haemolytic disease of the new born. Some few were Rh negative mothers discovered by routine examination.

(a) 12 cases proved not to have been sensitized by previous pregnancy. In five (heterozygous husbands) the first child had been Rh negative. In four other cases the babies showed progressive anaemia by the fourth to eighth week.

(b) 15 cases showed hydrops foetalis, maceration, death *in utero*, or premature still-birth. Antibody was demonstrated in four cases, while two cases showed anti-rh combination without demonstrable antibody.

(c) Eight cases had live-born babies which died of clinical haemolytic disease of the new born before treatment could be given. In two cases antibody was demonstrated.

(d) Two cases with previous histories suggesting haemolytic disease of the new born and with heterozygous husbands, achieved Rh negative babies. To these must be added six cases successfully but unnecessarily transfused, because it was subsequently proved that the baby was Rh negative. Thus eight babies in the series fall into this group.

(e) Four cases proved impossible of successful transfusion. Three had demonstrable antibody and died. One without antibody lived. This case will be featured later.

(f) 26 cases (plus two primiparous cases with antibody) showed the babies successfully transfused.

It is of importance to study in more detail these 28 cases of successful transfusion of the babies.

Four of the cases had repeated transfusion. Three were anticipated and one not anticipated.

All four cases showed demonstrable antibody.

Two survived (one the non-anticipated case) and two died.

Of the other 24 transfused once only, 18 were anticipated and six not so.

Of five that died, antibody was detected in four.

Of 19 that lived, antibody was proved in five cases, while in six cases transfused at birth the transfusion was afterwards proved unnecessary because the baby was Rh negative, the same genotype as the mother.

Thus 13 successes can be claimed out of 24, and 15 out of 28 cases.

So, of 55 cases of proved or expected haemolytic disease of the new born, 33 babies perished. Of the 22 survivors, 21 were transfused, six unnecessarily, and in the other one transfusion was impossible, a net result of 15 successes at the utmost.

Of this series of 100 cases (33 primipara, 67 multipara), 22 cases showed antibody, incomplete antibody, or atypical antibody. Of the 22 cases, 18 babies were born alive and 13 were transfused. Seven babies survived, six died after transfusion, two died before transfusion could be managed, and in three transfusion was unsuccessfully attempted. All 11 babies that died showed either proved or clinical kernicterus. The husbands' genotypes in these 22 cases are as follows:—

Homozygous	19— R_1R_1 (10), R_1R_2 (8), R_2R_2 or R_2r (1) (5 babies alive).
Heterozygous	2— R_1r (1 baby alive).
Anti-rh	1—(baby alive).

In this series, in 27 multiparous cases with rr mothers, the babies showed clinical manifestations of haemolytic disease of the new born, but no antibody was ever demonstrable. These also must be studied in detail.

Eleven babies died prematurely of hydrops foetalis, maceration, death *in utero*.

The fathers proved homozygous in ten cases (R_1R_1) five, (R_1R_2) five and heterozygous (R_1r) in the 11th.

In six cases death of the baby anticipated treatment. The fathers' genotypes were (R_1R_1) four and (R_1R_2) two.

Eight cases were transfused successfully, and lived, with fathers' genotypes of (R_1R_1) two, (R_1R_2) four and (R_2R_2 or R_2r) two.

One died after transfusion (father R_1R_1) and one lived after failure to transfuse. In four of the babies that died kernicterus was proved by autopsy.

In the series four Caesarean sections were performed. One was a third operation for contracted pelvis, in which the history suggested two previous foetal deaths from haemolytic disease of the new born. The child was transfused at birth, but proved Rh negative the same as the mother, and so transfusion was unnecessary. The other three cases were planned Caesarean sections at 38th week because of detected antibody in the mothers' serum. One baby had repeated transfusion, the other two did not survive long enough to have more than one. All three died of kernicterus.

Illustrative Cases

A. SENSITIZED PRIMIPARAE

Mrs. E.L. (Anticipated case).

	Born	Blood	Anti-Rh
Mrs. E.L.	..	O rr	
Mr. L.	..	$A_1 R_1 r$	
Baby	.. 1946	$A_1 R_1 r$	
Transfusion first day— $\frac{1}{2}$ pint Rh neg. blood.			
After this Hb 120 per cent.			
Blood picture:—			
Early primary erythroblasts	..	2 per cent.	
Late primary erythroblasts	..	15 per cent.	
Normoblasts	..	2 per cent.	

At eight weeks Hb. 62 per cent. Gradually rose on increased doses of anahaemin and iron by mouth.

Six months Hb. 68 per cent.

This baby has not been attending for routine examination and treatment, and typifies the recurrence of anaemia that may happen about the sixth month of life.

Mrs. R.A.K. (Anticipated case).

Born Blood

Mrs. R.A.K. A rr Trace antibody.

Mr. K. B R₁R₂

Baby 1946 B R₂r

Transfusion first day— $\frac{1}{2}$ pint Rh neg. blood.

Four weeks Hb. 92 per cent.

Nine weeks Hb. 66 per cent.

With increased doses of anahaemin and iron rose to 94 per cent. at four months.

B. NON-SENSITIZED MULTIPARAE

Mrs. L.A.

Born Blood

Mrs. L.A. B rr

Mr. A. A R₁r

Sheila AB rr

Baby 1946 O R₁r Normal, female.

Note that first baby was Rh negative.

Mrs. S.B.

Born Blood

Mrs. S. B. O rr

Mr. B. B R₂R¹

Beryl O R¹r

Baby 1946 B R₂r

At six weeks Hb had fallen to 62 per cent.

With anahaemin and iron Hb. had risen to 90 per cent. at four months.

This typifies the marked and progressive anaemia that may occur in some non-sensitized cases.

C. CASES SHOWING HYDROPS FOETALIS, MACERATION, DEATH *in utero*

Mrs. A.B. (Anticipated case).

Born Blood

Mrs. A.B. 1907 A₁ rr

Mr. B. 1907 A₁ R₁R₂

1930

Full term. Normal delivery. Alive and well.

1933 A₁ R₁r

Full term. Normal delivery. Alive and well.

1937

Full term. Normal delivery. Lived 15 minutes.

1938

Full term. Normal delivery. Icterus neonatorum. Died third day.

1940

Full term. Normal delivery. Macerated.

1941

Full term. Normal delivery. Still-birth.

1943

32 weeks. Normal delivery. Still-birth.

1944

Full term. Normal delivery. Still-birth.

1945

Premature still-birth.

Mrs. C.N.T. (Anticipated case).

Born Blood

Mrs. C.N.T. 1908 O rr Incomplete antibody 1 : 2.

Mr. T. 1897 B R₁R₁

1930

Full term. Still-born.

1934

3/12 abortion.

1935 B R₁r

Full term. Normal delivery. Alive, mentally unsound.

1937

Full term. Macerated.

1939

36 weeks. Macerated.

1943

36 weeks. Macerated.

1945

Induced 36 weeks. Macerated.

Mrs. I.A.N. (Non-anticipated case).

Born Blood

Mrs. I.A.N. 1909 O rr Anti-Rh (1 : 16,000)

Mr. N. 1908 O R₁R₂

Jean 1928 O R₂r

Full term. Normal delivery. Alive and well.

Mary 1931 O R₂r

Full term. Normal delivery. Alive and well.

Violet 1932 O R₁r

Full term. Normal delivery.

1940

Full term. S.B.

1944

Full term. Normal delivery. Jaundice 3rd day, lasted 14 days. Alive and well.

1945

S.B. Macerated. 34 weeks.

Admitted with puerperal sepsis and P.P.H. transfused with matched blood; transfusion reaction after a few ccs. Matched blood proved Rh positive. Packed cell transfusion of Rh negative blood given successfully.

Mrs. M.L. (Non-anticipated case).

1936

Caesarean section
at term. Baby
jaundiced, lived
1 day.

Born Blood

Mrs. M.L. .. 1921 O rr Incomplete anti-
body 1 : 2.

Mr. L. .. 1915 B R₁R₂
1942 O R₂r Full term. Normal
delivery. Alive
and well.

1945 Foetus died in
utero.

1945 O rr

Caesarean section
at term. Alive
and well.

Transfused at birth— $\frac{1}{2}$ pint Rh negative blood.
An unnecessary transfusion.

Mrs. J.C. (Anticipated case).

Born Blood

Mrs. J.C. .. O rr

Mr. C. .. B R₂R₂ or
R₂r

1944

Normal delivery.
Stillborn.

1946 O rr

Alive and well.

Transfused at birth— $\frac{1}{2}$ pint Rh negative blood.
An unnecessary transfusion.

D. BABIES BORN ALIVE, BUT WHICH DIED BEFORE TRANSFUSION COULD BE AFFECTED.

Mrs. B.P. (Non-anticipated case).

Born Blood

Mrs. B.P. .. 1916 A₁ rr Anti-Rh 1 : 16.

Mr. P. .. 1911 O R₂R₂ or
R₂r

Female .. 1939 A₁ R₂r Induction at term
for pre-eclampsia. Alive and
well.

Male .. 1944 O R₂r No jaundice at
birth. Slight
jaundice 1st day.
Deep jaundice
and dead 3rd
day.

Autopsy—kernicterus.

Mrs. D.R. (Non anticipated case).

Born Blood

Mrs. D.R. .. 1923 O rr

Mr. D.R. .. 1922 O R₁R₁
1943

Full term. Normal
delivery. Alive
and well.

1944 O R₁r, Full term. Normal
delivery. Jaun-
diced at birth.
Died 2nd day.

Clinical signs of kernicterus.

Baby's serum showed traces of antibody.

Autopsy—haemolytic disease of the new born.

At no time could antibody be demonstrated in
mother's blood.

E. Rh NEGATIVE MULTIPARAE MATED WITH HETEROZYGOUS HUSBANDS WITH PREVIOUS HISTORY SUGGESTING HAEMOLYTIC DISEASE OF THE NEW BORN, BUT WHO ACHIEVED AN Rh NEGATIVE CHILD.

Mrs. C.F. (Anticipated case), contracted pelvis.

Born Blood

Mrs. C.F. .. 1913 O rr

Mr. F. .. 1908 O R₁r

1934

Caesarean section
at term. Baby
jaundiced, lived
2 days.

1940

Full term. Normal
delivery. Jaun-
diced, died 5th
day.

1942

Full term. Normal
delivery. Jaun-
diced, died 5th
day.

G. REPEATED TRANSFUSION WITH UNSUCCESSFUL RESULTS

Mrs. V.S. (Anticipated case).

Born Blood

Mrs. V.S. .. 1917 A₁ rr

Anti-Rh 1 : 256.

Mr. S. .. 1916 O R₁R₁
1938

Full term. Normal
delivery. Jaun-
diced, died 5th
day.

1940

Full term. Normal
delivery. Jaun-
diced, died 5th
day.

1942

Full term. Normal
delivery. Jaun-
diced, died 5th
day.

Mrs. J.D.J. (Anticipated case).

Born Blood

Mrs. J.D.J. .. A rr

Anti-Rh 1 : 8

Mr. J. .. A R₁r

Rose .. 1943 O R₁r

Alive and well.

Richard .. 1944 A R₁r

Jaundiced at birth.
Transfused.
Alive and well.
37-38 weeks. Jaun-
diced at birth.
Died 2nd day.

1946

Baby S. .. 1943 A R₁r Full term. Normal delivery. Jaundiced, died 4th day.

Transfused first day—200 ccs. Rh negative blood, third day—200 ccs. Rh negative blood.

Autopsy—kernicterus.

Breast milk showed anti-Rh (1 : 16).

Mrs. D.M.C. (Anticipated case).

Born Blood

Mrs. D.M.C. 1912 A₁ rr Incomplete antibody 1 : 1.

Mr. S.O.C. ... 1910 O R₁R₁

J.S.C. ... 1942 A₁ R₁r Jaundiced at birth. Transfused with father's blood daily for a week. Alive and well.

Baby C. ... 1945 A₁ R₁r Planned Caesarean section. Died 4th day.

Transfused 1st day—60 ccs. Rh negative blood, second day—25 ccs. Rh negative blood.

Autopsy—haemolytic anaemia.

H. SUCCESSFULLY TRANSFUSED, BUT DIED

Mrs. H.B. (Non-anticipated case).

Born Blood

Mrs. H.B. ... 1914 A rr Anti-Rh 1 : 1.

Mr. B. ... 1914 O R₁R₁

1938 Full term. Normal delivery.

1940 Full term. Normal delivery. Jaundiced 4 weeks.

1945 A R₁r Full term. Normal delivery. Jaundiced 2nd day. Died 4th day.

Seen fourth day—clinical kernicterus.

Transfused with Rh negative blood, $\frac{1}{2}$ pint.

Mrs. M.B. (Non-anticipated case).

Born Blood

Mrs. M.B. ... 1912 A₂ rr Traces Anti-Rh.

Mr. B. ... 1913 A₁ R₁R₁

1933 Alive and well.

1937 Alive and well.

1939 Developed jaundice 3rd day. Paralysed.

1944 A₁ R₁r Jaundice appeared 2 hours and deepened rapidly. Died 3rd day.

Transfused second day— $\frac{1}{2}$ pint Rh negative blood.

Clinical signs of kernicterus.

I. TRANSFUSED SUCCESSFULLY, WITH BABIES ALIVE AND WELL.

Mrs. R.A.R. (Non-anticipated case).

Born Blood

Mrs. R.A.R. 1919 O rr Agglutinin present but demonstrable at room or refrigeration temperature only.

Mr. R. ... 1918 A R₁R₂

1943 Alive and well.

1945 A R₁r Normal delivery.

Jaundice and marked anaemia 2nd day. Blood film consistent with diagnosis of icterus gravis neonatorum.

Transfused second day with 100 ccs. Rh negative blood. Still marked jaundice and anaemia.

Transfused third day with 200 ccs. Rh negative blood. Fifth day—Hb. 80 per cent. Seventh day—Hb. 65 per cent.

Transfused with 130 ccs. Rh negative blood seventh day. Ninth day—Hb. 85 per cent. Eleventh day—Hb. 70 per cent.

Transfused eleventh day with 100 ccs. Rh negative blood. Thirteenth day—Hb. 100 per cent.

Anahaemin and iron dosage persisted with. At four weeks—Hb. 68 per cent.

Transfused with 250 ccs. Rh negative blood. Two days later—Hb. 85 per cent. At eight weeks—Hb. 70 per cent.

Massive doses of anahaemin and iron persisted with. Hb. percentage gradually rose.

At six months of age—Hb. 96 per cent. Blood picture entirely normal.

This baby is now a healthy and apparently normal child.

Mrs. K.F. (Non-anticipated case).

Born Blood

Mrs. K.F. ... O rr

Mr. F. ... O R₁r

1942 O R₁r Alive and well.

1946 O R₁r

Baby seen fifth day suffering from icterus gravis neonatorum.

Transfused same day—240 ccs. Rh negative blood. After this Hb. 106 per cent.

Three weeks—Hb. 56 per cent. Transfusion unsuccessfully attempted.

Four weeks—Hb. 52 per cent. Small transfusion via anterior fontanelle.

Intensive anahaemin and iron persisted with.

Six months—Hb. 100 per cent.

Mrs. E.J.G. (Anticipated case, via routine examination).

	Born	Blood
Mrs. E.J.G.	O rr	Anti-Rh 1 : 4.
Mr. G.	O R ₁ R ₂	
	1941 O R ₁ r	Alive and well.
	1946 O R ₂ r	

Transfused at birth—240 ccs. Rh negative blood. After this Hb. 154 per cent.

Four weeks, Hb. 84 per cent.—anahaemin and iron commenced.

Eight weeks, Hb. 62 per cent.—treatment intensified.

Five months, Hb. 96 per cent.

Six months, Hb. 86 per cent.

This typifies the anaemia which may recur about the sixth month of life.

J. ANTI-rh REACTION

Mrs. C.B. (Anticipated case).

	Born	Blood
Mrs. C.B.	1908 A ₁ R ₁ R ₁	
Mr. B.	1905 O rr	
	1933	Abortion 3/12.
	1934	Died <i>in utero</i> before term.
	1942	Abortion 6/12.
	1946	Abortion 5/12.

No antibody demonstrated.

Mrs. P.E. (Anticipated case).

	Born	Blood
Mrs. P.E.	1916 A ₁ R ₂ R ₂ or R ₂ r	
Mr. E.	1921 A ₁ rr	
	1943	Surgical induction at 34 weeks for anencephaly.
	1945 A R ₂ r	Induction 32 weeks for anencephaly.

No antibody demonstrated.

Mrs. N.P. (Anticipated case). Infantile paralysis as a child.

	Born	Blood
Mrs. N.P.	1905 A ₁ R ₁ R ₁	Anti-rh 1 : 8.
Mr. P.	1908 O R ₁ r	
	1944	S.B. 36 weeks breech.
	1945 R ₁ r	Extended breech, induced 39th week, due to sharp rise in titre of antibody.

Transfusion at birth—140 ccs. R₁R₁ blood. Jaundice appeared second day, deepened rapidly. Deep jaundice fifth day, cleared at tenth. Child gaining weight, but getting transparently anaemic. Hb. 120 after transfusion. Fell rapidly despite

anahaemin $\frac{1}{2}$ cc. daily plus ferri et ammon. cit. Two weeks, Hb. 75 per cent. ; Three weeks, Hb. 62 per cent. Transfusion 270 ccs. R₁R₁ blood. Hb. 85 per cent. ; Five weeks, Hb. 65 per cent. Transfusion 280 ccs. R₁R₁ blood. Hb. 82 per cent., fell quickly to 72 per cent. but no lower, and then gradually rose (anahaemin and iron given continuously). Eight weeks, Hb. 88 per cent. Differential count normal.

Twelve weeks, Hb. 76 per cent.

Fourteen weeks, Hb. 72 per cent. Anahaemin intensified 1 cc. daily. Haemoglobin gradually rose, baby kept gaining weight.

Twenty-four weeks, Hb. 92 per cent. Blood picture normal.

Thirty-six weeks, normal child developing well.

Note :—This is the fourth discovered case of anti-rh antibody, and joins Levine's anti-Hr, Taylor's Stead (St), and Stanbury's Tong.

K. MOTHER SENSITIZED BY PREVIOUS TRANSFUSION.

Mrs. M.

	Born	Blood	Anti-Rh in low titre.
Mrs. M.	O rr		
Mr. M.	O R ₁ R ₁		
T.	O R ₁ r		
A.	O R ₁ r		
C.	O R ₁ r		
M.	1945 O R ₁ r		
I.	1946 O R ₁ r		Icterus gravis neonatorum.

Seen fourth day. Transfused same day—250 ccs. Rh negative blood. Anahaemin and iron commenced.

Four weeks, Hb. 75 per cent. but gradually rose to 92 per cent. by four months. Mrs. M. had severe P.P.H. after fourth child and was transfused with 2 pints of type 4 blood. No reaction of any kind occurred. It is possible that this case falls into the class sensitized by transfusion. On the other hand, it may be sensitization to the husband's R₁ delayed longer than is usual.

L. DEBATABLE CASES.

When an Rh negative woman is married to a homozygous male, with genotype of different positive allelomorphs, e.g. R₁R₂, R₁R¹, it seems possible for her to be sensitized to one positive gene, and yet produce an unaffected child when the other gene enters into combination.

Mrs. O.A. (Anticipated case).

	Born	Blood
Mrs. O.A.	O rr	
Mr. A.	A R ₁ R ₂	
	1930 A R ₁ r	
	1933	Stillbirth at 36 weeks.
	1935	Abortion 2 months.

1937 Abortion 6 weeks.
 1946 A R₂r
 Two attempted transfusions failed.
 Eight weeks, child anaemic—Hb. 66 per cent.,
 treated with anahaemin and iron.
 Seven months—Hb. 100 per cent.

Mrs. W.L.P. (Anticipated case).

	Born	Blood	
Mrs. W.L.P.		rr	No antibody.
Mr. P.		R ₁ R ₂	
	1943		Full term. Spina bifida.
	1944		Premature 30 weeks. Died 8 hours.

1946 R₂r
 Transfused at birth with Rh negative blood. A pint was given by error.

Fourth day, Hb. 190 per cent. Seven million R.B.C. per cub. cm.

Eighteenth day, Hb. 125 per cent.

Three months, Hb. 93 per cent. Normal blood count.

Six months, Hb. 92 per cent. Normal blood count.

It is probable that this was also an unnecessary transfusion.

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Summary and Conclusions

(a) When a mother has been sensitized by a birth definitely affected by isoimmunization to the Rh factor, it will be noted that early abortion is apt to occur in subsequent pregnancies. So far, there is no proof that the Rh factor is a cause of abortion without previous isoimmunization having occurred. So many cases of repeated early abortion in

childless women have been noted, however, where it was theoretically possible for the Rh factor to be involved, that there seems to be a field still open to wider research.

(b) For reasons at present unknown, haemolytic disease of the new born does not occur in all and every case where it can be anticipated, or where it is possible for it to do so. In other words, it is not known why isoimmunization occurs in some families and not in others.

(c) The sooner transfusion of the child follows its birth the better. An unnecessary transfusion, pending the determination of the baby's genotype, is worth while doing, but must not be claimed as a success.

(d) The future will bring Rh factor investigation in all cases of pregnancy. The factor also has an obvious medico-legal significance.

(e) Thinking people in future will have their genotypes established before marriage. Maybe the time will come in this world when as much care, thought and trouble will be taken over the breeding of the human species as is taken over the breeding of animals.

(f) The problem is still in the melting pot, and the practical application of Rh factor will, of necessity, modify as research advances.

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