THE Rhesus Story in Northern Ireland

by

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In the last four decades the Rhesus problem has been defined; its cause then identified, leading on to a rational treatment which for a time was available to the baby after birth but later extended to the baby before birth; culminating in the grand finale—disease prevention. Unfortunately that grand finale, despite the optimism of the seventies, had not yet been reached.

Discovery of the Rhesus Blood Group

For many years, doctors had realised that there was a heterogeneous group of newborn babies who developed jaundice, anaemia or both, which were variants of a single underlying disorder, characterised by haemolysis and erythroblastosis. In 1940, Landsteiner and Wiener\(^1\) published a paper of less than 20 lines in which they described the discovery of the Rhesus blood group system. In the following year Levine\(^2\) reported that haemolytic disease of the newborn or in some cases a stillbirth, was due to incompatibility between mother and fetus.

The next developments took place in England where Fisher,\(^3\) working in Cambridge, predicted and later proposed an alternative notation to the Rh/hr suggested by Wiener. His CDE/cde notation is now accepted throughout the world. Coombs,\(^4\) working in the same laboratory, developed a technique for detecting Rhesus antibodies. This test is also used throughout the world.

Seventeen per cent of women in the British Isles are Rhesus negative, and lack of this antigens is designated by the letters d/d. It has been calculated\(^5\) that three of the seventeen will marry Rhesus negative husbands, six will marry homozygous Rhesus positive (D/D) husbands with a 1:12 chance of the second child being affected, while eight will marry heterozygous Rhesus positive (D/d) husbands with a chance of the second baby being affected in 1:15.

Clinical Background

Before the introduction of Rhesus prophylaxis the incidence of the disease was 1:200 of all pregnancies. Rhesus negative women became sensitised during the first pregnancy, usually during the third stage of labour as the placenta separated. Minor degrees of placental separation may occur during pregnancy, e.g., threatened abortion, antepartum haemorrhage during external cephalic version and amnio-centesis, and play a part in the sensitisation of a small number of patients. Following sensitisation, in any subsequent pregnancy, if the fetus is Rhesus positive, antibodies will be produced. Formerly, blood transfusion had been a major factor in the production of antibodies. Donald\(^5\) reported that pre-1950 over one-third of all patients with antibodies gave a history of blood transfusion.

For many years the only treatment available was a direct transfusion of blood to the baby after birth—often the father's Rhesus positive blood being used! Rhesus negative blood was given after its discovery. Wallestein\(^6\) in New York described the
first "exsanguination-replacement" transfusions. In this procedure he inserted one needle into the superior sagittal sinus and a second needle into the umbilical vein. The "exchange" transfusion as performed today only became a reality after the development of the plastic tubing and its introduction into medical practice. In 1947, Diamond brought samples of tubing to Britain and introduced the exchange transfusion. The first such transfusion was performed in Belfast in 1948.

The perinatal mortality remained high so premature induction of labour was considered as another means of improving the results. The Medical Research Council initiated a multicentre controlled trial into the management of patients with antibodies. Two problems were considered—1) the routine induction of premature labour at three or five weeks before term versus the onset of spontaneous labour, and 2) exchange transfusion versus direct transfusion to the baby. Northern Ireland was represented on the supervising committee by Dr W.A.B. Campbell and all patients in the Belfast teaching hospitals were used in the trial. The results are shown in Table I. The authors concluded that babies born spontaneously at term had a lower mortality than those born prematurely and that exchange transfusion was a better form of treatment than simple direct transfusion.

| Table I |
|---|
| Results of M.R.C. trial 1952. Fetal loss due to Rhesus disease |
| Exchange transfusion | 13.0% |
| Direct transfusion | 37.0% |
| Routine induction of labour | 36.4% |
| Spontaneous onset of labour | 24.1% |

THE LOCAL SCENE

In July 1948, the National Health Service was established. No consultant obstetricians had been based outside Belfast nor were maternity beds available apart from those in the Belfast hospitals. Thus, in 1948, there were only 12 patients with antibodies delivered in the Royal Maternity Hospital, Belfast. The importance of centralisation and the need for paediatric help was obvious. As consultant obstetricians were appointed to peripheral hospitals, patients with antibodies were transferred to Belfast for treatment. In 1956, 63 patients with antibodies had been delivered in the Royal Maternity Hospital, and 15 babies born elsewhere admitted for treatment, while in Jubilee Maternity Hospital 32 patients were delivered and 6 infants transferred for treatment.

Professor C.H.G. Macafee did not accept the results of the MRC trial and instead advocated a policy of selective induction of premature labour. His views were supported by Kelsall and Vos who reported a loss of only 10.7 per cent in infants delivered by premature induction of labour, compared with a loss of 23.4 per cent in those delivered spontaneously at term. Fisher published a series from Royal Maternity Hospital which showed that selective planned induction of labour—as distinct from the MRC routine induction of labour—resulted in a lower fetal loss of
16 per cent as compared with 29 per cent in a similar group delivered at term (Table II). Fisher also pointed out that those infants delivered following induction of labour were from mothers with a bad Rhesus history and required twice as many exchange transfusions as those delivered at term. Campbell\textsuperscript{12} reported that a high potassium level in stored citrated blood had toxic effects on many babies during exchange transfusion and recommended that freshly collected heparinised blood should be used for the exchange transfusion.

| TABLE II |
| Fetal loss due to Rhesus disease, Royal Maternity Hospital, Belfast, 1957 |
| Selective induction of labour | 16.0% |
| Spontaneous onset of labour | 29.0% |

In selecting patients for induction of labour, Professor Macafee admitted such women not later than the thirty-sixth week of the pregnancy. The indications for induction were, to a certain extent, arbitrary, e.g., the history of a previously affected or stillborn infant due to haemolytic disease, a rising antibody titre and a homozygous Rhesus positive father were important factors. During the latter weeks of pregnancy any diminution of fetal movements reported by the patient or an alteration in the fetal heart noted by the midwife were indications for immediate delivery.

CONTINUING RESEARCH

Obviously there was a need for a specific test to help in selecting patients for induction of labour. In 1950, Bevis\textsuperscript{13} in Manchester commenced studies on the liquor obtained by hindwater rupture at the time of induction of labour. In 1956\textsuperscript{14} he reported that measurement of the bilirubin content of the liquor obtained by amniocentesis during the pregnancy was the best indicator of fetal wellbeing. This test has become the yardstick by which the severity of the disease is measured. The test was improved by Liley\textsuperscript{15} who in turn produced the results on a graphic form in which the degree of severity of the affected fetus was recorded in three zones—mild, moderate and severe. Amniocentesis in the management of patients with antibodies was introduced in the Waveney Hospital by Vernon Parry,\textsuperscript{16} a former colleague of Bevis.

Amniocentesis is not without risk. In a series of 410 amniocenteses performed prior to placental localisation, Peddle\textsuperscript{17} reported that transplacental haemorrhage from fetus to mother occurred in 11.2 per cent. Placental localisation by ultrasound reduces the risk. In the Royal Maternity Hospital, in 1977, despite the use of ultrasound, transplacental haemorrhage was reported in 20 out of 128 amniocenteses performed on women with antibodies. Obviously, in these 20 patients this diagnostic test made the condition worse.

The diagnosis of transplacental haemorrhage could only be made after the introduction of a technique to demonstrate fetal cells in the maternal blood.\textsuperscript{18} This test was perfected but was not specifically described in the management of Rhesus patients. Zipursky\textsuperscript{19} in Winnipeg was the first to apply this test to maternal blood after delivery.
OTHER TREATMENT

About the late 1950’s phototherapy was introduced into the management of the babies. This treatment followed the observation of a ward sister who noted that jaundice faded quickly in those babies who had been exposed for a short time to sunlight. Though there seems no doubt that this is true, the consensus of opinion seems to be that the therapy is of more benefit in jaundice associated with prematurity than in that due to Rhesus disease.20

Liley21 published details of the use of intra-uterine fetal transfusion in an effort to prevent stillbirth or the delivery of very severely affected babies. This procedure was enthusiastically adopted in many centres. In 1964 the first such procedure was performed in Jubilee Maternity Hospital, Belfast.22 In the following year the first intra-uterine transfusion was performed in Royal Maternity Hospital.23

In an attempt to protect the baby from high levels of antibodies while in utero the technique of plasmapharesis was introduced. The results are difficult to evaluate, as other methods of treatment are also given simultaneously, e.g., intra-uterine fetal transfusion. It is possible, however, that repeated plasmapharesis lowers the affinity of the Rhesus antibody and this may explain the apparent success of the procedure.24 The method was not found rewarding in Belfast.

In 1968, Whitfield25 introduced his “Action Line” which was superimposed on Liley’s zones. While Liley had predicted the severity of the disease, different managements of the patient were advocated by various workers. Whitfield based his recommendation on the results of two bilirubin estimations. This was later modified26 when liquor studies of the lecithin sphingomyelin area ratio (LSAR) became available. This test is used to estimate the maturity of the fetal lungs. Obviously, if the result was good the baby could be delivered knowing that there would be no respiratory problems in addition to the haemolytic problem. Likewise, if the test was poor then intra-uterine fetal transfusion was needed. The number of intra-uterine transfusions in Royal Maternity Hospital is shown in Table III. The dramatic fall is due mainly to the changes in management and the virtual disappearance of the “grand multipara”.

| Year | Transfusions | Patients |
|------|--------------|----------|
| 1966 | 6            | 6        |
| 1970 | 88           | 55       |
| 1975 | 17           | 13       |
| 1981 | 1            | 1        |

PROPHYLAXIS

The extraordinary story of how an amateur interest in butterflies which had led Clarke27 to start work on genetics which eventually turned from butterflies to the human blood groups is well known. This led to the discovery that fetal Rhesus-positive cells in the maternal blood could be destroyed by administering anti-D in the
form of gammaglobulin to the mother in the puerperium. At about the same time in the United States of America, Freda et al.\textsuperscript{28} were achieving similar clinical results, although they had arrived at their conclusions by a different route. Their story is no less bizarre—using volunteers from Sing-Sing Prison as their original subjects.

Routine prophylaxis by the injection of 100 mg of anti-D gammaglobulin within 72 hours of delivery to a Rhesus negative woman who had been delivered of a Rhesus positive baby was introduced in 1970.\textsuperscript{29} In 1968 this was given to selected patients following delivery. This was due to the small volume of supplies available. Only in 1971 was routine prophylaxis made available here to all women who required this treatment. The dramatic fall in the number of women with antibodies delivered in Royal Maternity Hospital is shown in Table IV. This is mainly due to prophylaxis but also to the ready availability of contraceptive advice.

\begin{table}
\centering
\caption{Patients delivered in Royal Maternity Hospital, Belfast}
\begin{tabular}{llll}
\hline
Date & Total & Affected & Fetal loss \\
\hline
1948 & 12 & 7 & 57\% \\
1955 & 67 & 54 & 31\% \\
1968 & 237 & 161 & 19\% \\
1975 & 116 & 65 & 26\% \\
1981 & 43 & 36 & 11\% \\
\hline
\end{tabular}
\end{table}

The Standing Medical Advisory Committee Report on the Prevention of Rhesus Disease\textsuperscript{30} recommended that anti-D be given after spontaneous abortions. This had not been the practice in Northern Ireland. An addendum recommending further indications for the use of anti-D is currently being considered. This would include indications such as routine prophylaxis after external cephalic version, etc.

Some women are still developing antibodies. McClelland and McLoughlin\textsuperscript{31} reported some disturbing figures from the province (Table V). Obviously, there is room for improvement as some of the patients did not receive anti-D. This applies particularly to those women who abort at home before their blood group is known and to those few women who are delivered at home. With the present methods it is accepted that prophylaxis will fail in 2 per cent of those women who have received

\begin{table}
\centering
\caption{Failures in Northern Ireland 1978-1979: Women with Rhesus antibodies}
\begin{tabular}{ll}
\hline
Failure of administration & 11 \\
Failure of treatment & 17 \\
Primigravidae & 2 \\
Uncertain & 1 \\
\hline
\end{tabular}
\end{table}
the gammaglobulin. In several countries this has been reduced by the administration of anti-D during the pregnancy. Figures from Canada, United States, Sweden and Australia show that the failure rate can be reduced to 0.2 per cent.\textsuperscript{32} However, the authors use varying quantities of anti-D and administer it at different times during the pregnancy. Their recommendations would require a fourfold increase in the amount of anti-D gammaglobulin required. In the United Kingdom, a further clinical trial, using anti-D during pregnancy is in progress in several centres.

OTHER RHESUS ANTIBODIES

There are a small number of patients with antibodies other than D. There is no prophylaxis against these. It is of interest that there has been no drop in the numbers. The patients from Royal Maternity Hospital have been discussed in detail.\textsuperscript{33} Anti-E has not been a problem but C and c antibodies may severely affect the fetus and the patients must be carefully supervised. It should be noted that these antibodies may be found in Rhesus positive patients. Obviously, as prophylaxis against the D antibody continues these others will eventually form the major part of the problem.

CONCLUSION

The story of the Rhesus disease is fascinating, especially as so much, from diagnosis to prevention, has taken place in a very short time. Doctors from many countries have contributed to this. The importance of “teamwork” has been shown—obstetrician, neonatologist, haematologist and physician combining to produce a good end result. Northern Ireland doctors have played an important role in influencing opinion in the United Kingdom.

Complacency must not develop while that “grand finale”—elimination of all anti-D antibodies—has not yet been achieved. We must continually be on our guard to ensure that anti-D gammaglobulin is always given when required and we await the recommendations of the present British research workers which will reduce the disease even further.

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