Rhesus haemolytic disease

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Rhesus (Rh) haemolytic disease has been greatly reduced in incidence by the prophylactic programme with anti-D immunoglobulin, but it will not be eliminated. Even with careful documentation and close liaison between medical, nursing and laboratory personnel, there are occasional failures to administer anti-D to Rh-negative women at risk of sensitization following either delivery (Crowle, 1974) or abortion, or after antenatal events which may be associated with transplacental fetomaternal bleeding, eg, amniocentesis, external version or placental abruption; there are also, of course, women who are already D-sensitized but have not yet completed their reproductive careers, while others have antibodies against Rh antigens other than D; very occasionally Rh sensitization may still result from the transfusion of mismatched blood. For these reasons, we will continue to see small numbers of pregnant women with Rh antibodies, but the multi-disciplinary teams responsible for their management and for the care of their babies will find it increasingly difficult to maintain practical experience and expertise. There is therefore a clear need to organize care on a regional basis.

In addition to obstetricians and paediatricians with special experience of this problem, multi-disciplinary Rh teams must include biochemists, haematologists and blood transfusion specialists, and also radiologists. They must be based on centres with full perinatal facilities, including a neonatal intensive care unit and facilities for both diagnostic ultrasound and intrauterine fetal transfusion.

Such a team was established in 1967 at the Royal Maternity Hospital, Belfast, where up to that time six consultant obstetricians had shared the responsibility for the supervision of about two-thirds of the Rh-immunized pregnant women in Northern Ireland, which province has a population of some one and three-quarter million persons, and where severe Rh haemolytic disease is a particularly common problem because of a tendency to very high parity even among women who have already had a succession of unsuccessful pregnancies.

Action Line Method

From 1 May 1967, coincident with the adoption of

the action line (AL) method of determining the optimal time for intervention—delivery or intrauterine transfusion—in Rh-immunized patients, it was agreed that all such patients should become the responsibility of a single 'Rh clinic' under the author's control. Thenceforth, an increasing number of women were referred to this clinic by their own family doctors and from other hospitals that no longer undertook the management of patients with antibodies: all these patients were classified as 'directly referred'. A small but decreasing number of other hospitals in Northern Ireland retained the majority of their Rh-immunized patients and referred only those in whom the baby was considered to be at very high risk on the basis of the outcome of previous pregnancies: these women were classified as 'transferred patients'.

Because the essential decision in managing pregnancy in Rh-immunized women is to select the optimal time for intervention, based on the presence, severity and likely further trend of haemolysis in the fetus as indicated by the trend of the amniotic fluid bilirubin concentration, our AL method (as originally described by Whitfield *et al* (1968), and subsequently extended by Whitfield *et al* (1970)) will be outlined.

Amniocenteses, which should be carried out under immediate ultrasonic control to locate both the placenta and a suitable collection of amniotic fluid, are timed in accordance with the previous Rh history. Thus, the first amniocentesis is performed 10 weeks before the time of the earliest previous fetal death due to Rh-incompatibility, or the earliest fetal transfusion or birth of a very severely affected infant, but not before 20 weeks' gestation because, even in the worst circumstances, intrauterine transfusion before about 23 weeks would not be considered. In the absence of such a previous history of very severe erythroblastosis, an initial amniocentesis between 28 and 30 weeks is usually followed by another at 32 or 33 weeks, but this optimal three- or four-week interval may be reduced or additional amniocenteses may be indicated when, for example, the bilirubin value is already very high or is rising sharply. The bilirubin concentration in the amniotic fluid is estimated by spectrophotometry using the

Fig 1 The action line as used throughout the first three-year series (1967-70) with the Δ OD at 450 $m\mu$ plotted (semi-logarithmic scale) against gestational age (weeks). When the Δ OD at 450 $m\mu$ is on or above the action line before 33 weeks (case A) or its trend extrapolates to that part of the line (cases B and C) intrauterine fetal transfusion is indicated. After 33 weeks a value beyond the action line calls for immediate delivery (case D), or extrapolation of the trend between separate measurements indicates the optimal time for delivery (cases E, F, and G). With values less than 0.035, amniocentesis is not repeated and term delivery is indicated.

method devised by Liley (1961) to measure the optical density deviation (Δ OD) at 450 $m\mu$, and this value is plotted on a logarithmic scale against gestation (in weeks). Instead of using prediction zones, such as those devised by Liley, the Δ OD at 450 $m\mu$ and the extrapolation of its trend between serial tests is related to the curved AL (fig 1) to determine when to intervene, the AL having been established following retrospective analysis of more than 100 pregnancies.

Up to 33 weeks, the AL indicates the need and time for intrauterine transfusion to avoid imminent fetal death, as in case A with an initial result already beyond the AL, and in cases B and C in which the fetuses were transfused when the extrapolated trends between separate Δ OD at 450 $m\mu$ measurements reached the line. It is not surprising that the AL between 27 and 33 weeks should almost coincide with the demarcation between Liley's top and middle prediction zones and also with the lower limits of the transfusion zones devised by Liggins (1966) and Robertson (1969). However, it is higher than the

critical levels used for transfusion at some other centres (Gordon *et al*, 1966; Little *et al*, 1966; Bowman *et al*, 1969) which in our own cases would have led to some unnecessary fetal transfusions, including several in fetuses which did not even need exchange transfusion following delivery at term.

In case E the initial Δ OD at 450 $m\mu$ value is actually higher than in case C, but a more favourable trend led us to deliver during the 37th week a baby with moderately severe haemolytic disease. It should be noted that in both these cases, because the initial value was near the AL amniocentesis was repeated within 10 days in case a rising trend would very soon reach the AL (as actually occurred in case C). Case D provides an example of a bilirubin trend rising steeply to beyond the AL, suggesting that acute haemolysis was likely to occur, and a severely affected baby with cord blood values of 6.4 mg of bilirubin and 11.0 g of haemoglobin per 100 ml was delivered without further delay. In case F the bilirubin trend, which was parallel to but lower than that in case E, extrapolated to the AL at 38 weeks when a mildly affected baby was delivered.

Amniotic fluid bilirubin values before 27 weeks are not usually in line with the trend during the last trimester. So, unless very early transfusion has already been indicated, extrapolation is based on additional tests after 27 weeks. Thus, in case G an unaffected Rh-negative baby was left safely *in utero* till term despite a previous history of two Rh stillbirths.

Term delivery is allowed, without further amniocentesis, when the Δ OD at 450 $m\mu$ is less than 0.035 as indicated by the horizontal broken line in fig 1. When antibodies first appear at 34 to 36 weeks a single test usually suffices; when they appear after 36 weeks amniocentesis is not necessary.

A practical advantage of the AL method over the use of prediction zones or other prediction criteria is that, instead of simply providing a forecast of the severity of the haemolytic process which must somehow be translated into a management policy, it determines the time when continued conservative management is no longer in the interest of the fetus. A further related advantage is that it avoids much unnecessary intervention and prematurity, by selecting for term delivery about three-quarters of all unaffected and mildly affected babies and indicating a continuation of pregnancy to at least 38 weeks in the remainder.

First Three-year Series (1967-70): Special Problems

As previously reported (Whitfield, 1970), in pregnancies managed along these lines during the three-year period from 1 May 1967 to 30 April 1970 there

were 76 Rh deaths among 666 babies, an Rh mortality rate of 11.4%, Rh deaths being defined as all abortions, stillbirths or neonatal deaths attributable or probably attributable to Rh incompatibility or its treatment, and also other deaths, eg, from prematurity, in which haemolytic disease or its treatment may have been a contributory factor. There was a total wastage (including abortions) from all causes of 13.4%. Exclusion of 25 very high-risk transferred patients (only six infants in this group eventually survived) leaves an Rh mortality rate of 8.9% for the 641 directly referred patients, which is comparable to the results reported from New Zealand by Liley (1963).

Following a detailed review of the results in this first three-year period of AL management, it was decided that in future particular attention should be paid to the following five problems: (1) the effect of abnormal amniotic fluid volume on the bilirubin concentration and on the prediction of severity; (2) the occasional unexpected occurrence of acute haemolysis in the fetus; (3) the risk of neonatal respiratory distress and hyaline membrane disease, particularly in babies born very prematurely after intrauterine transfusion; (4) the further development of our standard fetal transfusion techniques; (5) the attempted reduction of extremely high maternal antibody levels by repeated plasmapheresis in early booking patients with histories of multiple previous Rh stillbirth, in an attempt to give some protection to the fetus until it provides a big enough target for intrauterine transfusion. In addition it was found administratively efficient to allocate all Rh-negative patients to the Rh clinic, and this policy was also of great value in ensuring that routine repeated antibody screening was always carried out and that anti-D prophylaxis was effective.

Amniotic Fluid Volume Measurements and Effect of Abnormal Volumes on Prediction

With regard to the possible effect of amniotic fluid volume upon bilirubin values, a simplified accurate amniotic fluid volume test using a para-aminohippurate (PAH) dilution test, with measurement by spectrophotometry rather than by the diazo reaction, was developed by Thompson *et al* (1971). Having next established tentative normal limits and trends from 200 measured amniotic fluid volumes in patients who were subsequently delivered of Rh-negative babies, during the next three-year period (1 May 1970 to 30 April 1973) the test became a routine procedure at each amniocentesis. As previously reported (Whitfield, 1971), most volume estimations in Rh-incompatible pregnancies are within the normal limits, although there are some

abnormally high volumes which are usually associated with severely or fatally affected infants. Serial results show the same unpredictable variation in trend that was found in association with unaffected fetuses. A clinical impression that rapidly developing polyhydramnios sometimes precedes hydrops fetalis was confirmed, although a rapid reduction in volume may occur just before the fetus dies.

There were several examples of increasing concentration of bilirubin that were probably due to decreasing amniotic fluid volume rather than to increasing haemolysis in the fetus, including at least one case in which intrauterine transfusion was performed probably unnecessarily; conversely, in five cases confirmation that an apparently favourable bilirubin trend was probably due to developing polyhydramnios provided a warning not to delay delivery of severely affected infants. Despite such occasional examples of the usefulness of amniotic fluid volume estimations, their value as a routine procedure at every amniocentesis remains doubtful and this policy has since been abandoned.

Antibody Protein Measurements and Acute Fetal Haemolysis

Accurate automated measurement of serum anti-D antibody protein, as described by Fraser *et al* (1972), was available during the second three-year period. It enabled us, by routine monthly testing (or more frequently if indicated), to detect sudden steep rises in the level of maternal antibody which are always ominous and which suggest that an acute fetal haemolytic crisis is about to occur. This occasional phenomenon may follow antibody 'boosting' by fetomaternal bleeding due to transplacental amniocentesis or associated with antepartum haemorrhage due to placental separation, but it is as likely to occur near term without obvious cause in which case immediate delivery is vital. Typically in such cases, there follows a very acute and continuing haemolysis resulting in cord blood bilirubin values usually above 5.0 mg per 100 ml and the need for multiple exchange transfusions at relatively short intervals.

Repeated measurements of antibody protein in more than 400 patients indicated that term delivery without amniocentesis is safe if specific antibody protein remains below 0.5 μ g per ml. On the other hand, particularly in first affected pregnancies, levels above 4.0 μ g per ml suggest that severe haemolytic disease is likely. These findings are in close agreement with those of Fraser and his associates. In addition, the finding by Fraser and Tovey (1972) that some improvement in prediction can be obtained by measuring antibody protein as well as bilirubin

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ml). In reporting this, Whitfield and Sproule (1974) described five examples of sharply falling lecithin:sphingomyelin ratios apparently associated with acute haemolysis in the fetus, suggesting that severe fetal anaemia may inhibit production and/or release of alveolar surfactant in the fetal lungs. Paradoxically, there were also abnormally high ratios in relation to some other very severely anaemic fetuses, in which it is speculated that there may have been an initial corticosteroid-induced response to stress.

Figure 3 illustrates the value of these three ancillary tests. In this patient, a marked rise in serum antibody protein suggested that a fetal haemolytic crisis was imminent; a third amniocentesis showed a sharp reversal in the initially favourable bilirubin trend and, because the virtually static amniotic fluid volume excluded the possibility that this might be due to developing oligohydramnios, intervention was indicated at 33 weeks as a matter of urgency; because the lecithin:sphingomyelin ratio was just satisfactory, the baby was delivered (rather than transfused *in utero*) then; both the unusually high cord bilirubin level and the extremely rapid development of deep jaundice confirmed the presence of very rapid haemolysis; the severely affected premature infant received two exchange transfusions and survived without respiratory complication.

Intrauterine Fetal Transfusion

The standard techniques used in Belfast for intrauterine fetal transfusion have been reported elsewhere (Whitfield *et al*, 1972).

Fetuses receiving 1 transfusion	127
Fetuses receiving 2 transfusions	68
Fetuses receiving 3 transfusions	23
Fetuses receiving 4 transfusions	8
Total of fetuses transfused	226
Total no. of transfusions given	364
Failed attempts	4 ¹
Fetal deaths within 12 hours of transfusion	49
Other fetal deaths	55
Neonatal deaths due to Rh disease	27
Total Rh deaths	131 (57.9%)
Neonatal deaths due to other causes	4
Total surviving infants	91 (40.3%)

Table I Details of intrauterine fetal transfusions during the combined six-year period, 1967-1973

¹Transfusions completed at further attempts in three of these cases; no further attempt in remaining case because anencephaly was recognized on radiographs.

During the two three-year study periods a total of 364 intrauterine transfusions was given to 226 fetuses and there were also four unsuccessful attempts at fetal transfusion. Of 1347 fetuses in directly referred patients, including some who, usually be-

cause of late reference to hospital, could not be managed by the methods outlined, 159 or 11.8%, were transfused *in utero*. The earliest fetal transfusion was at 23 weeks' gestation and 28 other fetuses were transfused by 25 weeks; six fetuses were transfused as late as 33 to 35 weeks (five because the amniotic fluid lecithin:sphingomyelin ratio was still less than 2.0). Other details are shown in table I, and the evidence for several practical lessons to be drawn from this experience is presented in tables II and III.

	No.	Eventual survivors
<i>Transfusion First Attempted¹</i>		
< 27 weeks	77	9 (11.7%)
27-30 weeks	72	31 (43.1%)
> 30 weeks	78	51 (65.4%)
Hydrops (generalized)	34	nil
Ascites (not hydropic)	56	25 (44.6%)
Neither	137	66 (48.2%)
<i>Maternal Complications</i>		
Infection	29	7 (24.1%)
Vaginal bleeding	28	15 (53.6%)
Spontaneous rupture of membranes	37	20 (54.1%)
Spontaneous labour before intended time	60	33 (55.5%)

Table II Factors relating to eventual survival following intrauterine fetal transfusion

¹Including the four unsuccessful attempts.

Ninety-one of the 226 transfused fetuses eventually survived, a survival rate of 40.3%, and they remain under long-term paediatric follow up which, so far, shows that they have developed physically and mentally exactly as would be expected from a comparable group of premature babies unaffected by haemolytic disease. Factors relating to survival include the time of the first transfusion, the presence of hydrops fetalis, defined as generalized oedema with obvious scalp oedema revealed by double-contrast amniography, or ascites, considered to be present if at least 10 ml of fluid is aspirated from the fetal abdomen immediately before a transfusion is given, and various maternal complications (table II). Because intrauterine transfusion is not without maternal risks, it has been abandoned when the fetus is frankly hydropic since, in our hands, none such has ever survived. On the other hand, the survival rate for non-hydropic babies with ascites (45%) is almost as good as that for fetuses with neither hydrops nor ascites (48%), and our surviving infants include several from whom between 300 and 500 ml of ascitic fluid was aspirated at their intrauterine transfusions. Attention is also drawn to the importance of intrauterine infection, which was usually soon followed by abortion or premature labour and was associated with a survival rate of only 24%, whereas vaginal bleeding or rupture of the mem-

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branes and/or premature labour (without pyrexia) were associated with survival rates of more than 50%. Transfusions should be repeated as scheduled even when the patient has had repeated, perhaps heavy, vaginal bleeding and even after the membranes have ruptured provided there is no evidence of infection.

	No.	Immediate Fetal Deaths
Difficult transfusions	80	26 (32.5%)
Other transfusions	284	23 (8.1%)
	364	49 (13.5%)
<i>Approach to Fetal Abdomen</i>		
Right lateral	75	18 (24.0%)
Left lateral	129	19 (14.7%)
Anterior	124	9 (7.3%)
Not recorded	36	3 (8.3%)
	364	49 (13.5%)

Table III Factors relating to 'immediate operative mortality' after intrauterine transfusion (fetal death within 12 hours)

Regarding the immediate operative mortality of the procedure (table III), which we define as fetal death within 12 hours of its completion, it is not surprising that this is directly related to technical difficulties in performing the transfusion. We also learned to enter the lower part of the fetal abdomen anteriorly whenever possible, if necessary by altering the fetal position but more often by using a widely angled approach through the maternal flank: it is in such cases that experienced teamwork by the obstetrician and radiologist really counts. Operative mortality varied from a rate of only 7% when the front of the fetal abdomen was entered to 15% when the fetal left flank was entered and 24% when the transfusion needle was passed through the right flank and presumably the enlarged fetal liver.

As previously reported (Whitfield *et al*, 1972), the estimated percentage of donor red cells from a single intrauterine transfusion persisting in the fetoplacental circulation at birth is greatest when delivery occurs during the second week after transfusion. At this stage in 54 babies we found that at least 80% of the transfused erythrocytes could be accounted for in the circulation, but there was a progressive reduction with a longer transfusion-delivery interval. The same data also confirmed that donor blood is usually very quickly absorbed from the fetal peritoneal cavity, one of our infants having apparently already absorbed 80% of the transfused red cells when it was born 44 hours later. Ascitic fetuses seem to absorb as much or almost as much donor blood as do non-ascitic infants, but liveborn hydropic babies have only very small amounts of donor blood in their circulation.

Intensive Plasmapheresis

Intensive plasmapheresis was first used as a therapeutic measure in Rh-immunized pregnant women in Liverpool (Clarke *et al*, 1970), and I am indebted to Dr Lehane of the Liverpool Regional Blood Transfusion Service for the following details (Lehane, 1972). Of 16 Rh-immunized and one Kell-immunized pregnant women treated by repeated plasmapheresis, in only five was this started before 20 weeks and in five it was continued during the last trimester; four women were delivered during the last month of pregnancy after having repeated plasmaphereses but not intrauterine transfusions and two of their babies were Coombs-negative. We were perhaps too reluctant in Belfast to use this approach, other than a rather desperate attempt to give some protection to the most severely affected Rh-immunized fetuses until they had grown sufficiently to present a feasible target for intrauterine transfusion. Eight of our patients with histories of several Rh stillbirths and with very high antibody levels had repeated plasmapheresis from the end of the first trimester until fetal transfusion became possible at 23 to 24 weeks, about 600 ml of plasma being removed on each of five days in every week. Spontaneous abortion occurred in one patient soon after this programme was started, six fetuses died with hydrops developing while plasmaphereses were still being carried out, and the only surviving infant required three intrauterine transfusions. These disappointing results, and the lack of any real evidence that antibody levels have been reduced, led us to abandon plasmapheresis as a therapeutic measure.

It is unfortunate that no adequate controlled trial of intensive plasmapheresis seems to have been carried out while there were still relatively large numbers of Rh-immunized pregnant women. A very recent report from Bristol and Liverpool describes considerable experience of plasmapheresis in mothers 'diagnosed as carrying babies severely affected with rhesus haemolytic disease', 44 of whom were treated by repeated plasmapheresis and fetal transfusions and a further 52 by plasmaphereses alone (Fraser *et al*, 1976) but it does not provide real evidence that the procedure is of therapeutic value. Not only do the authors of that report not indicate their diagnostic criteria for severe haemolytic disease, either *in utero* or at birth, or how they define hydrops fetalis, but their claim for the efficacy of intensive plasmapheresis rests largely on a strange belief that 'only 10% of mothers with a previous history of stillbirths have a successful outcome in the next pregnancy'. In fact, better results following previous stillbirths were reported even before the introduction of amniocentesis and intrauterine transfusion (Walker and

Category	Previous Affected Infants	First Series (1967-70)				Second Series (1970-73)			
		Fetuses		Rh deaths		Fetuses		Rh deaths	
		No.	Percentage of Series	No.	Rate (%)	No.	Percentage of Series	No.	Rate (%)
A	None	357	53.6	13	3.6	316	44.8	6	1.9
B	Alive: no exchange transfusions	80	12.0	5	6.25	121	17.1	8	6.6
C	Alive: at least 1 exchange transfusion	148	22.2	14	9.5	159	22.5	26	16.3
D	At least 1 Rh death	81	12.2	44	54.3	110	15.6	43	39.1
All patients		666		76	11.4 ¹	706		83	11.8 ¹
Transferred patients from other Rh centres		25		19		153		21	
Directly referred patients		641		57	8.9	553		62	11.2

Table IV *Rhesus mortality rates in all correctly managed patients during the two series (1 May 1967 to 30 April 1970, and 1 May 1970 to 30 April 1973) illustrating effect of previous Rh history and showing Rh mortality rates for directly referred patients separately*

¹Total wastage (including abortions) from all causes was 13.4% in first series, and 13.6% in second series.

Murray, 1956) and, as shown in the present report, survival rates of around 50% can be achieved in such patients by centralized intensive multidisciplinary care. Similarly, the survival at Bristol and Liverpool of 17 out of 27 babies (63%) of mothers with a previous history of severely affected or 'hydropic' babies is matched in the second three-year series in Belfast even when only mothers with previous Rh deaths are considered, 36 out of 102 babies (65%) surviving, without plasmapheresis.

Comparison of the Results in the Two Series (1967-70 and 1970-73)

It was disappointing that the additional measurements and refinements described, while contributing to the salvage of some critically affected babies, did not lead to an overall improvement in survival. Thus, as table IV shows, the Rh mortality rate in all AL-managed patients was virtually the same during the second three-year series as during the first (11.8% compared with 11.4%), as was total wastage from all causes (13.6% compared with 13.4%), while the Rh mortality rate in directly referred patients actually increased (11.2% compared with 8.9%).

However, by classifying patients in accordance with the outcome of their previous pregnancies, ie, the 'Rh history', table IV also shows that there was also a significant change in pattern between the two series which largely explains the apparent failure to reduce perinatal mortality. Thus, due to the introduction and increasing implementation of anti-D prophylaxis, there were fewer women with antibodies for the first time (category A, which as a group carries the lowest perinatal risk) and Rh mortality was halved in them from a rate of 3.6 to 1.9%. There were also rather more women with histories of previous Rh deaths in the second series, and the Rh mortality rate in this group (category D)

was reduced from 54.3 to 39.1%. There were similar proportions of patients whose previous affected infants had survived with exchange transfusions (category C) in the two series, but Rh mortality was actually higher in this category during the second series—16.3% compared with 9.5%. In fact this itself reflects the efficacy of increasing intensive obstetric and neonatal management in that the preceding pregnancies of most such patients in the second series had also been intensively managed, whereas many otherwise exactly equivalent patients in the first series were in category D, having had unsuccessful preceding pregnancies before the introduction of the AL methods and before the increasing centralization of Rh management (when the overall Rh mortality rate was almost 20%). Also, because of the adoption of stricter indications for initial neonatal exchange transfusion and a reduction in the need for repeat exchange transfusions as a result of phototherapy, many relatively low-risk pregnancies in category C in the first series would have been in category B (previous affected infants surviving without exchange transfusion) had they occurred during the second series, leaving category C as a generally less favourable group.

One very striking improvement achieved during the second series was the reduction in the number of neonatal deaths due to the combined effects of haemolytic disease and severe respiratory distress. Thus, although 20 out of 666 AL-managed babies had died in this way in the first series (including eight who had been transfused *in utero*) only seven out of 706 in the second series did so, two having had intrauterine transfusions.

It can therefore be concluded that intensive centralized management at regional Rh centres is of value, especially in the high-risk patients of category D and, at the other end of the prognostic spectrum, also in first affected pregnancies. With regard to the

latter, there seems to be insufficient awareness that the first Rh-affected baby in a family may be critically or fatally affected, and that as Liley (1961) pointed out 'the first stillbirth or neonatal death should be the easiest and best one to avoid'. It may be the only one that can be avoided as is well illustrated by 39 mothers whose first affected infants died from Rh disease and came under our care during their next Rh-positive pregnancies from which only eight infants (21%) survived.

If the inevitable continued loss of Rh-incompatible babies is to be minimized, there must be full implementation of the national programme for anti-D prophylaxis, which is based on a standard dosage of 100 µg for mothers at risk of sensitization following completion of Rh-positive pregnancies after 20 weeks and half of this dose when abortion occurs before 20 weeks. Apart from the need for a 'fail-safe' system to ensure that prophylaxis is always implemented, two problems need special attention.

First, in relation to antenatal sensitization, it is not always realized that prophylaxis, with Kleihauer testing to determine the required dose of immunoglobulin, should be extended to as yet unsensitized Rh-negative women undergoing amniocentesis (unless perhaps ultrasound has clearly shown that the placenta has been avoided) or external version, or when placental abruption is suspected.

Secondly, there are certain circumstances in which large transplacental haemorrhages, that should be dealt with by giving an increased dose of immunoglobulin, are likely to occur and may well cause such severe sensitization that the next Rh-positive baby is critically or fatally affected. Sufficient information was available to be certain that such very severe sensitization had occurred in 81 patients. Only 18 of their sensitizing pregnancies were completely normal (22%), and the importance of placental abruption or fulminant preeclampsia, multiple delivery or caesarean section, and manual removal of the placenta as

potentially strongly sensitizing events is demonstrated in table V.

Finally, it must not be forgotten that comprehensive Rh-prophylaxis must also include the informed counselling of parents after any pregnancy in which antibodies were present. Such counselling is based on careful assessment of the perinatal risks in a future pregnancy, according to the previous history in relation to the husband's probable Rh-genotype, and it must of course be supported by an effective contraceptive service.

References

- Borer, R. C., Jr., Gluck, L., Freeman, R. K., and Kulovich, M. V. (1971). Prenatal prediction of the respiratory distress syndrome (RDS). (Abstr.) *Pediat. Res.*, **5**, 655.
- Bowman, J. M., Friesen, R. F., Bowman, W. D., McInnis, A. C., Barnes, P. H., and Grewar, D. (1969). Fetal transfusion in severe Rh isoimmunization. *J. Amer. med. Ass.*, **207**, 1101-1106.
- Clarke, C. A., Elson, C. J., Bradley, J., Donohoe, W. T. A., and Lehane, D. (1970). Intensive plasmapheresis as a therapeutic measure in rhesus-immunized women. *Lancet*, **1**, 793-798.
- Crowle, P. M. (1974). An analysis of the efficiency of a rhesus haemolytic disease prophylaxis programme. *Brit. J. prev. soc. Med.*, **28**, 101-103.
- Fraser, I. D., Bothamley, J. E., Bennett, M. O., Airth, G. R., Lehane, D., McCarthy, M., and Roberts, F. M. (1976). Intensive antenatal plasmapheresis in severe rhesus isoimmunization. *Lancet*, **1**, 6-9.
- Fraser, I. D., and Tovey, G. H. (1972). Estimation of antibody protein in amniotic fluid to predict severity in rhesus haemolytic disease. *J. Obstet. Gynaec. Brit. Cwlth*, **79**, 981-984.
- Fraser, I. D., Tovey, G. H., Lockyer, W. J., and Sobey, D. F. (1972). Antibody protein levels in the maternal serum in rhesus isoimmunization. *J. Obstet. Gynaec. Brit. Cwlth*, **79**, 1074-1079.
- Gordon, H., Grausz, J. P., Raphael, M., and Browne, J. C. M. (1966). Experience with intraperitoneal transfusion. *J. Obstet. Gynaec. Brit. Cwlth*, **73**, 917-922.
- Lappin, T. R. J. (1973). Personal communication.
- Lehane, D. (1972). Personal communication.
- Liggins, G. C. (1966). Current indications for intrauterine transfusion. In *Proceedings of the 53rd Ross Conference: Intrauterine Transfusion and Erythroblastosis Fetalis*, edited by J. F. Lucey and L. J. Butterfield, pp. 28-33. Ross Laboratories, Columbus, Ohio.
- Liley, A. W. (1961). Liquor amni analysis in the management of the pregnancy complicated by rhesus sensitization. *Amer. J. Obstet. Gynec.*, **82**, 1359-1370.
- Liely, A. W. (1963). Intrauterine transfusion of foetus in haemolytic disease. *Brit. med. J.*, **2**, 1107-1109.
- Little, B., McCutcheon, E., and Desforages, J. F. (1966). Amniocentesis and intrauterine transfusion in Rh-sensitized pregnancy. *New Engl. J. Med.*, **274**, 332-335.
- Robertson, J. G. (1969). Management of patients with Rh isoimmunization based on amniotic fluid examination. *Amer. J. Obstet. Gynec.*, **103**, 713-722.
- Thompson, W., Lappin, T. R. J., and Elder, G. E. (1971). Liquor volume by direct spectrophotometric determination of injected PAH. *J. Obstet. Gynaec. Brit. Cwlth*, **78**, 341-344.
- Walker, W., and Murray, S. (1956). Haemolytic disease of the newborn as a family problem. *Brit. med. J.*, **1**, 187-193.

Sensitizing Pregnancy	No.
Normal	18 (22.2%)
Acute preeclampsia	13 (16.0%)
Placental abruption	10 (12.3%)
Multiple delivery (all twins)	10 (12.3%)
Caesarean section (all lower segment)	13 (16.0%)
Manual removal of placenta	24 (29.6%)
	88 ¹

Table V Details of sensitizing pregnancies in 81 patients in whom the next Rh-positive fetus was affected fatally or critically (cord blood haemoglobin < 8.0 g per 100 ml)

¹Multiple factors present in four patients, eg, placental abruption complicating fulminant preeclampsia in patient delivered by Caesarean section.

- Whitfield, C. R., Neely, R. A., and Telford, M. E. (1968). Amniotic fluid analysis in rhesus iso-immunization. *J. Obstet. Gynaec. Brit. Cwlth*, **75**, 121-127.
- Whitfield, C. R., Lappin, T. R. J., and Carson, M. (1970). Further development and experience in an action line method for the management of rhesus iso-immunization. *J. Obstet. Gynaec. Brit. Cwlth*, **77**, 791-795.
- Whitfield, C. R. (1970). A three-year assessment of an action line method of timing intervention in rhesus isoimmunization. *Amer. J. Obstet. Gynec.*, **108**, 1239-1244.
- Whitfield, C. R. (1971). Effect of amniotic fluid volume on prediction. *Clin. Obstet. Gynec.*, **14**, 537-547.
- Whitfield, C. R., Thompson, W., Armstrong, M. J., and Reid, M. McC. (1972). Intrauterine fetal transfusion for severe rhesus haemolytic disease. *J. Obstet. Gynaec. Brit. Cwlth*, **79**, 931-940.
- Whitfield, C. R., and Sproule, W. B. (1974). Fetal lung maturation. *Brit. J. hosp. Med.*, **12**, 678-690.