Papers and Originals

Intrauterine Transfusion in Rh-isoimmunization

D. V. I. FAIRWEATHER,*|| M.D., F.R.C.O.G. ; D. TACCHI,* M.D., F.R.C.O.G. ; A. COXON,† M.B., M.R.C.O.G.
M. I. HUGHES,‡ M.B., CH.B. ; S. MURRAY,‡ M.D., M.R.C.P., F.C.PATH. ; W. WALKER,§ M.D., M.R.C.P., M.C.PATH.

Brit. med. J., 1967, **4**, 189–194

Fifteen per cent. of all cases of Rh-isoimmunization end in stillbirth. Until 1963 the only available means of preventing this outcome in cases with a high risk of stillbirth was to deliver the foetus prematurely before intrauterine death had occurred. The value of this was limited, because many intrauterine deaths due to haemolytic disease of the newborn occur early in pregnancy, and because in the event of a live birth prematurity is a serious danger.

The introduction of intrauterine transfusion (Liley, 1963) offered the possibility that intrauterine life could be prolonged to a stage where premature induction could be more successfully employed, but implicit for its success and justification is a reliable forecast of the possible stillbirth and of the probable time of intrauterine death.

The present communication describes our selection of patients for intrauterine transfusion and our experience of the procedure as employed in the Newcastle hospitals during 1965 and 1966.

Selection of Patients

The final decision to carry out intrauterine transfusion depends on the level of bile pigment in the liquor amnii. Amniocentesis, however, involves risks, and to discriminate those patients in whom this procedure is justified use is made in the first place of the previous obstetric history.

Selection of Patients for Liquor Examination

At the first visit a patient can be placed in one of four categories:

(1) Patients currently developing antibodies—that is, first affected cases. The risk of stillbirth is only 8%, but this group comprises 60% of all cases. In these, intrauterine death tends to occur late in pregnancy, only 30% occurring before 37 weeks' gestation.

(2) Patients who have already had an affected infant who required no treatment. These families represent 10% of the total and carry no greater risk of stillbirth than pregnancy generally.

(3) Patients who have already had an affected infant who required transfusion. These families constitute 20% of the total ; the risk of stillbirth is increased to 20%, but 40% of the stillbirths occur before 37 weeks' gestation.

(4) Patients who have already had a liveborn hydropic infant or a stillbirth due to haemolytic disease. This is the history in 10% of cases ; the risk of a subsequent stillbirth if the foetus is Rh-positive exceeds 50%, and early intrauterine death often occurs. Walker (1960) estimated that after one previous stillbirth 50% of subsequent stillbirths occur in utero before 35 weeks, but after more than one stillbirth 50% die before 32 weeks' gestation.

If allowance is made for the size of and risk of stillbirth in each group it is calculated that the three groups carrying a significant risk of stillbirth contribute equally to the total stillbirths.

In 1965 and 1966 amniocentesis was carried out initially at approximately 22 weeks where previous stillbirth or very severe disease had occurred, at 32 weeks when there had been previous moderate disease, but at 35 weeks in first affected cases and only if the antibody titre exceeded 1/16 by indirect Coombs test. Liquor examination was usually repeated at intervals of two to three weeks.

Selection of Patients for Intrauterine Transfusion

There are many methods for estimating bilirubin in liquor, but we (Knox *et al.*, 1965 ; Savage *et al.*, 1966) have found that for predicting stillbirth at 34–36 weeks' gestation the critical liquor ratio $\frac{\text{transmission 520 m}\mu}{\text{transmission 490 m}\mu}$ is 1.06. As the bilirubin level in liquor tends to fall as pregnancy advances it was appreciated that a higher ratio would have to be adopted earlier in pregnancy, and a level of 1.1 was arbitrarily chosen.

To assess the reliability of this criterion and the value of intrauterine transfusion we decided to carry out a controlled trial in 1965. Patients were admitted to the trial if the liquor ratio exceeded 1.1 early in pregnancy, but final selection for or against intrauterine transfusion was random.

In 1966 we discontinued the trial and were able to improve selection for intrauterine transfusion to include only those cases where the liquor ratio early in pregnancy was 1.1 or higher on two consecutive occasions and was not falling.

Our experience also enabled a second group of patients to be included for intrauterine transfusion—namely, those with a single ratio exceeding 1.1 at about 32 weeks. Previous to intrauterine transfusion such patients would probably have been induced at 32 weeks' gestation, but combining such serious prematurity with severe haemolytic disease had resulted in almost a 40% neonatal mortality. In comparison, in patients induced at 35 weeks the neonatal mortality is under 20% and after spontaneous delivery at term just over 2%. It was also appreciated that the technique of intrauterine transfusion is much easier at 32 than at 22 weeks' gestation.

Material

In 1965 16 patients were admitted to the trial and in seven intrauterine transfusion was carried out within two weeks of the initial liquor examination. Provided the foetus survived, intrauterine transfusion was repeated at intervals of two to three

* Princess Mary Maternity Hospital, Newcastle upon Tyne.
† Newcastle General Hospital. Newcastle upon Tyne.
‡ Regional Blood Transfusion Centre, Newcastle upon Tyne.
§ Reader in Paediatric Haematology, University of Newcastle upon Tyne.
|| Present address: University College Hospital, London W.C.1.

weeks until delivery, which in all cases was induced prematurely. The nine patients not selected for intrauterine transfusion also had repeated liquor examinations until delivery, which was also induced prematurely.

In 1966 28 patients with a high and rising bilirubin level were selected for intrauterine transfusion, which was carried out within three weeks of the initial examination. Intrauterine transfusion was repeated at intervals of two to three weeks until delivery by premature induction. Another 17 patients also had amniocentesis, but, either because the bilirubin level did not meet the criteria or very early intrauterine death occurred, they were excluded from intrauterine transfusion. Liquor examination in these also was repeated at intervals of two to three weeks where appropriate until delivery.

Technique of Intrauterine Transfusion

Before the initial amniocentesis placental location is carried out by percutaneous femoral arteriography (or by radioisotope scanning) to reduce the risk of placental damage.

We feel it is important to extend to the mother in advance an adequate explanation of the programme to be followed and of the technique. One hour before the transfusion she is sedated with Omnopon 1/3 gr. (22 mg.) and scopolamine 1/120 gr. (0.5 mg.) and is then transferred to the *x*-ray department, where the operation is carried out under local anaesthesia. By using an image intensifier and television screen radiation is kept to a minimum and a Videotape recorder allows playback for reassessment without adding to screening time. The detailed steps are as follows:

(1) We find it a valuable aid, especially for the earlier transfusions —that is, at 24 and 26 weeks' gestation—to take a flat *x*-ray picture, by means of an under-couch tube, of the mother's abdomen with a marker on the umbilicus, when she is positioned for the transfusion. Within five minutes, after automatic processing, the dry film can be placed over the abdomen like a map, helping accurate palpation of a small foetus and enabling site and direction of puncture to be marked on the skin.

(2) With full aseptic technique, and after local anaesthesia, the Tuohy needle is introduced into the amniotic sac and a specimen of liquor is taken. The needle is then advanced until the foetal peritoneal cavity is entered.

(3) To ensure that the needle is not in solid tissue 1 ml. of saline is injected, then 2–5 ml. of Hypaque 45% (sodium diatrizoate) is injected. Sometimes the classical pattern of demilunes is seen, confirming the correct siting of the needle, but we have found the outline of the foetal diaphragm to be more helpful, though it often takes longer to develop.

(4) When we feel certain that the peritoneal cavity has been entered, a fine epidural catheter is introduced through the Tuohy needle and the latter is withdrawn. Before any transfusion aspiration is carried out to remove as much of the radiopaque material as possible, but also to remove any ascites or residual blood that may be present. Ascitic fluid, being clear and bright yellow, can usually be distinguished from liquor, which tends to be paler and cloudy. If necessary the nature of the fluid is confirmed by estimating the protein content by a sulphosalicylic acid method.

(5) A three-way tap is connected to the epidural catheter and donor blood, which is connected to the tap by a Baxter disposable giving set, can be drawn into a 10-ml. syringe and slowly injected into the foetus. Because concentrated red cells are used and the catheter is fine, we have found it necessary to compress the syringe by means of a modified screw clamp. The closed circuit minimizes risk of infection.

(6) Liley (1963) originally recommended injection of 100 ml. of blood, but we attributed three deaths, at 26 weeks' gestation, which occurred shortly after the procedure to the injection of too large a volume, and have now found the following routine more satisfactory: 24 weeks 30 ml., 26 weeks 45 ml., 28 weeks 60 ml., 30 weeks 80 ml., 32 weeks and later 100 ml. Approximately five minutes is taken to inject 10 ml. of blood.

(7) On completion of the transfusion 50,000 units of crystalline penicillin and 100 mg. of streptomycin mixture in 2 ml. is injected down the catheter and into the needle track as the catheter is withdrawn. We do not undertake routine antibiotic administration to the mother subsequently, and we have not as yet left catheters in situ between transfusions. No case of infection occurred.

Technique has been kept as simple as possible, and we have not found it necessary to inject radiopaque substance into the liquor in order that it may be swallowed to outline the foetal alimentary tract; nor do we think it wise to inject dye into foetal soft tissues to act as a marker.

We have not adopted Liggins's (1966) method of using a second needle to impale and steady the foetus during puncture of the foetal abdomen.

Selection of Blood for Intrauterine Transfusion

Appreciating that erythrocytes might be damaged by injecting through a fine catheter and by contact with radiopaque dyes, two preliminary experiments were carried out:

(1) Both time-expired and fresh blood concentrated to have a haematocrit of 80% was injected through the catheter at rates varying from 30 seconds to 10 minutes per 10 ml. The injected blood was then mixed with an equal volume of saline, and after centrifugation haemolysis in the supernatant was measured. Significant haemolysis occurred at all rates exceeding three minutes per 10-ml. injection. The potassium levels predictably were higher in rapidly injected blood, being on average 9 mEq when injected at the rate of three to seven minutes per 10 ml., compared with 18.4 mEq at 30 to 45 seconds per 10 ml.

(2) The blood having been injected through the catheter was mixed with radiopaque dyes in varying dilutions, and incubated at 37° C. for 2, 12, 24, and 72 hours. The amount of haemolysis in the mixture was estimated and the sample examined for spontaneous agglutination and assessed for reliability of ABO grouping. One part dye to 60 of blood was anticipated in the peritoneal cavity at intrauterine transfusion and at this dilution Myodil (iophendylate injection) caused 90% haemolysis in 72 hours and the remaining cells showed abnormal ABO grouping. Neo-Hydriol (iodized oil injection) gave similar results but is not recommended by the makers for intrauterine transfusion. Conray 480 (sodium iothalamate) caused spontaneous agglutination, false ABO grouping, and some haemolysis after as little as two hours' incubation. With Hypaque 45%, however, there was only a small amount of haemolysis even at 72 hours with a 1/60 or 1/30 dilution, but in higher concentration, particularly with Hypaque 66%, agglutination and some haemolysis did occur.

We have therefore used Hypaque 45% in minimal quantity, and before injecting blood have aspirated as much of the dye as possible. Like Liley (1965) we have found little evidence that Hypaque causes serious peritoneal reaction, though in two cases where it was accidentally injected into the thigh pronounced tissue necrosis occurred possibly causing temporary partial femoral artery occlusion in one infant. Deliberate injection of dye into soft tissue should be avoided.

Because delivery was not anticipated for several weeks after transfusion red cells not older than 48 hours have been used. To avoid the theoretical risk of injecting large numbers of viable lymphocytes red cells have been recovered from the bottom of bottles, avoiding the buffy layer, and we have preferred blood collected into acid citrate dextrose rather than into heparin. Concentrated red cells (haematocrit about 80%) minimize risks to the anaemic infant, including the injection of excess potassium or citrate.

Group O cde/cde blood was used for all cases, and care was taken to exclude donors with anti-A or anti-B haemolysins. Full compatibility tests with the mother's serum were performed, and in a number of patients selection has been difficult because of the presence of multiple antibodies.

By taking into account the ABO, Rh, and MNSs groups of the mother and father, it has usually been possible to select blood distinguishable from that of the parents, and sometimes from another donor used for a subsequent transfusion. We have thus, and by the Kleihauer *et al.* (1957) technique, been

able to identify and quantitate donor blood in the foetus at delivery and also in blood that may have escaped into the liquor or been retained in the peritoneal cavity or other sites in the foetus.

Accidents

Accidents with the procedure, despite careful technique, do occur, though these decrease as the operator becomes more experienced. Sites other than the peritoneal cavity may be entered, and in this series of 77 intrauterine transfusions the pleural cavity has been entered on two occasions, the pericardium once, the gastrointestinal tract twice, and the bladder three times. In no instance did this appear to cause any immediate trouble, and six of these eight infants were subsequently born alive with no apparent sequelae.

On one occasion we think the liver was punctured, and on resiting the needle in the peritoneal cavity 25 ml. of foetal blood was aspirated previous to the intrauterine transfusion. The infant was born 10 days later and survived. There was a puncture wound over the liver with extensive skin bruising. Extensive haemorrhage from the liver has been described (Gordon *et al.*, 1966), and may prove fatal.

On one occasion the spleen was probably entered, and though the foetus was stillborn it did not appear that the accident was responsible for the intrauterine death.

On seven occasions a small amount of foetal blood was obtained at the time of intrauterine transfusion, but only on the one occasion referred to did it exceed 1 ml.

The possibility that injection of blood into the peritoneal cavity might lead to adhesions and subsequent intestinal obstruction would seem plausible, and in two infants born alive after intrauterine transfusion there was evidence of partial intestinal obstruction in the neonatal period, but this responded to conservative treatment and did not result in permanent sequelae. In one stillborn foetus small adhesions between loops of bowel were shown at necropsy.

In three instances large collections—up to 50 ml.—of donor blood have been found in the musculature of the abdominal wall, which may have resulted from leakage from the peritoneal cavity, foetal bleeding, or because of the oedematous state of the foetus the injection being actually made into the abdominal wall.

Results in 1965

Though eight cases were selected for intrauterine transfusion, in one case the procedure was withheld because of a steadily falling liquor ratio after the 24th week, and an Rh-negative infant was born. Ten intrauterine transfusions were performed on the remaining seven patients, four receiving a single transfusion and three receiving two transfusions.

Table I shows 28% survival in the transfused group compared with 66% in those not transfused. The erroneous impression that intrauterine transfusion is of no value was brought about in two ways. The cases selected for intrauterine transfusion were, by chance, much more severely affected than those not selected, based on the retrospective observations that the first liquor ratios were higher in the treated group (average ratio 1.37) than in the untreated cases (average ratio 1.18). Also, in the untreated group were the two patients with Rh-negative infants and two infants with only moderate disease. Secondly, early difficulties encountered with the technique probably contributed to some of the deaths in the treated cases. However, valuable information accrued from the trial. Thus experience with the technique seemed to lead to better results, and an important point learnt was that the injection of 100 ml. of packed cells into a small foetus may precipitate death. Further, liquor findings showed that in all cases where a normal or only a moderately affected infant resulted there had been a fall in liquor ratio between the first and second test; whereas almost without exception pregnancies resulting in stillbirth or very severe disease showed an increase in ratio between the two tests.

TABLE I.—*Intrauterine Transfusion* 1965 *Trial*—Newcastle*

	Intrauterine Transfusion	
	Yes	No
Stillborn	4	2
Liveborn haemolytic disease of newborn — Neonatal death	1	1
Liveborn haemolytic disease of newborn — Alive	2	4
Coombs negative	0	2
Total	7 (10 transfusions)	9
Survival	28%	66%

* All patients included where previous history of stillbirth or very severe disease nd liquor ratio > 1·1 at 24–32 weeks.

That a normal infant may be associated with a high liquor ratio in early pregnancy is illustrated in Fig. 1, which shows cases resulting in Rh-negative infants and where at least three observations were carried out. In normal pregnancy the liquor ratio before 24 weeks may exceed 1.1; up to 30 weeks it may exceed 1.06, but after 33/34 weeks the ratio is usually below 1.04.

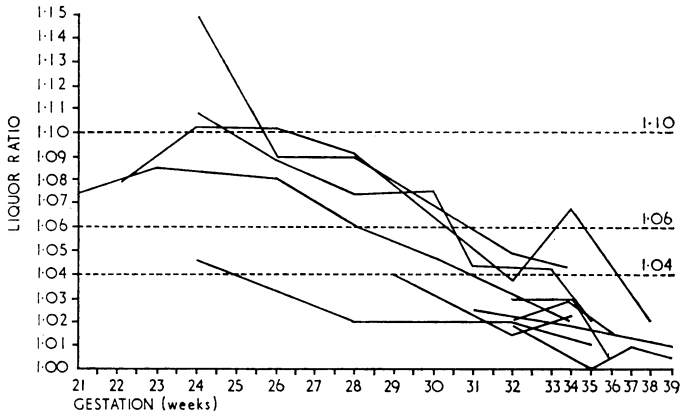

FIG. 1.—Repeated liquor examinations in Rh-negative pregnancies.

Results in 1966

The 28 patients selected under the revised criteria received 67 intrauterine transfusions (Table II). The overall survival rate was 54%. In 9 of the 11 stillborn cases death occurred very shortly after the first intrauterine transfusion, and in each case ascites had been detected at the transfusion. However, ascites was also present on at least one occasion in 12 of the 16 liveborn infants. Two of these infants had ascites tapped on two occasions, one on three, and one infant on no fewer than four occasions, a total of 160 ml. being removed. This infant was not hydropic at birth and survived.

TABLE II.—*Intrauterine Transfusion* 1966—*Newcastle*

Stillborn	11	10 with ascites found at I.U.T.
Liveborn haemolytic disease of newborn — Neonatal death	2 (1)	12 with ascites found at I.U.T.
Liveborn haemolytic disease of newborn — Alive	14 (4)	
Coombs negative	1 (1)	
Total	28 (67 transfusions)	
Survival	54%	

Numbers in parentheses are of cases where first transfusion was after 31 weeks.

Only six of the patients were selected for intrauterine transfusion after 30 weeks' gestation, and of particular interest is one infant who at operation had 110 ml. of ascites withdrawn before transfusion was carried out. Ten days later the infant was born alive; no donor cells were detected in the circulation; the cord haemoglobin was 38%, and though the infant had generalized oedema no significant ascites was present.

The one Rh-negative foetus transfused was wrongly selected, but it is probable that the calculated E.D.D. was incorrect and that liquor examination had been at 28 rather than at 32 weeks' gestation; allowance for this would have excluded selection. At birth the cord haemoglobin was 140% and 50% of the cord cells were donor cells. The infant (weight 4 lb. 6 oz.; 1,980 g.) developed hyperbilirubinaemia of prematurity requiring exchange transfusion, also respiratory distress, but survived.

Sixteen of the 17 patients producing liveborn infants in 1966 had labour induced between 35 and 37 weeks' gestation. One patient came into spontaneous premature labour at 35 weeks—16 days after the last (fourth) intrauterine transfusion. In the present series only one patient (3.6%) went into premature labour as a result of the procedure. In this case there was technical difficulty with the third intrauterine transfusion; the foetal bowel was entered, and when the catheter was finally properly sited, the needle having been removed, it was found to be blocked. The procedure was then abandoned. The next day the foetal heart was absent, and two days later labour began and a stillborn macerated infant was delivered.

During 1966 a further 19 patients were considered but not selected for intrauterine transfusion. In six the foetus had already died by 24 weeks' gestation. Of the remaining 13, excluded on liquor examination, five infants were Rh-negative and five were born alive between 36 and 42 weeks. Three were stillborn, two from causes other than haemolytic disease (one with placental insufficiency and cord prolapse, the other was an intrauterine death showing no obvious cause). The third stillbirth occurred where the mother's serum contained multiple antibodies (anti-D, anti-A_1, anti-Fy^a, anti-E, and a weak unspecified antibody). Though compatible blood for mother or infant was eventually found, it was thought expedient to reserve this for this time of delivery.

Severity of Disease in the Liveborn Infant

Nineteen affected infants were born alive after intrauterine transfusions. Some of the infants, owing to the presence of almost 100% Rh-negative donor cells, failed to show a positive direct Coombs test, while others gave a weak result. However, in these latter, where a few Rh-positive foetal cells—for example, 5% of the sample—are coated with a strong antibody, the pattern of Coombs test is quite different from the weak positive test due to many Rh-positive foetal cells being coated with a weak Rh antibody (see Fig. 2).

Cord haemoglobin values varied from 18 to 140%, and the proportions of adult and foetal blood are shown in Fig. 3.

It will be seen that the donor blood contribution to the cord haemoglobin at birth varied from 0 to 100%. The average cord haemoglobin was 66%, with 40% donor blood and 26% foetal blood. This represents severe disease, for the mean cord haemoglobin value in unselected cases of haemolytic disease is 100%. We failed to rationalize the amount of donor blood present at birth, even taking into account the size of the foetus and the number of donor cells injected, and allowing for estimated red cell survival. While this probably represented a failure of absorption in certain cases, several times donor blood has been recovered from the liquor. We think that occasionally a leakage back from the foetal peritoneal cavity occurs.

Eight infants were severely affected and treated within half an hour of birth, one having a cord haemoglobin of 18%, all of which was donor blood. Nine infants were moderately affected and were treated within nine hours and two, though not meeting our criteria for exchange transfusion, required simple transfusion later.

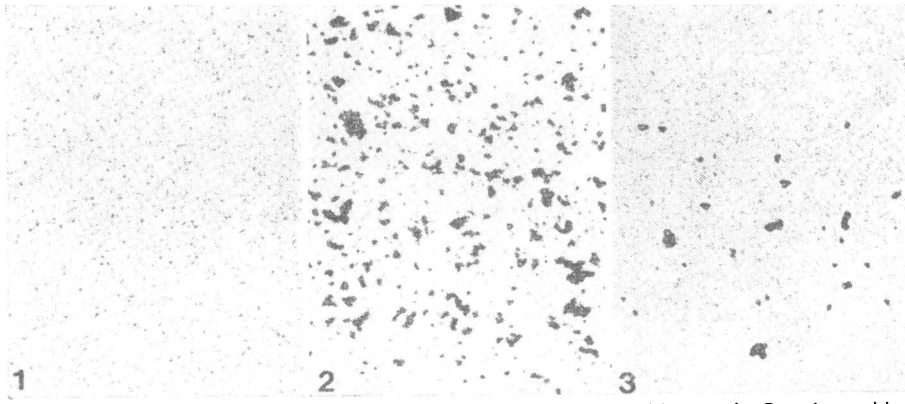

FIG. 2.—Direct Coombs test on (1) weakly Coombs positive infant; (2) strongly Coombs positive infant; and (3) infants after intrauterine transfusions with 20% foetal cells.

Cord bilirubin levels also indicate increased severity in these infants after intrauterine transfusion, with a range of 1.9 to 7.1 mg., and a mean of 4.2 mg., compared with a mean of 3 mg. in unselected material.

All of these infants were delivered prematurely, usually at about 35 weeks' gestation, and this policy is reflected in the birth weights, which ranged from 3 lb. 12 oz. (1,700 g.) to 7 lb. 5 oz. (3,315 g.), with a mean of 5 lb. 4 oz. (2,380 g.). Four infants were delivered by caesarean section because of failed induction, and a further three were delivered by caesarean section for other reasons (placenta praevia, foetal distress, unfavourable cervix). Six infants required resuscitation, though in only two was there prolonged difficulty in establishing respiration. Five infants developed respiratory distress, which was severe in two.

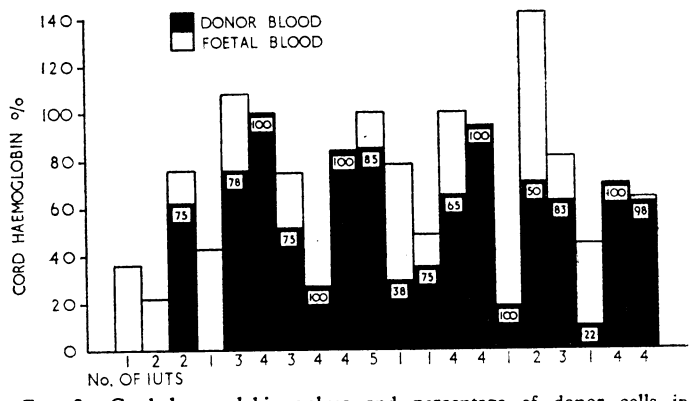

FIG. 3.—Cord haemoglobin values and percentage of donor cells in intrauterine transfusion cases.

Six infants required two exchange transfusions, while one required four. We did not find, as has been reported in the literature (Bowman, 1966; Work *et al.*, 1966), that exchange transfusion was required frequently in cases treated by intra-

uterine transfusion. In such reports, however, many patients came into premature labour shortly after intrauterine transfusion, and possibly continued absorption, after birth, of donor cells from the peritoneal cavity aggravated the hyperbilirubinaemia (Fong, 1966).

Simple transfusion was required in 10 cases, a much higher incidence than in haemolytic disease of similar severity not treated by intrauterine transfusion. The prolonged anaemia may be due to depression of the bone marrow consequent on intrauterine transfusion. One infant with a cord haemoglobin of 28%, nearly all of which was donor blood, had a reticulocyte count of only 1% ; and another with a cord haemoglobin of 18%, all donor blood, had a reticulocyte count of only 2%. One infant, who after five intrauterine transfusions required two simple transfusions, did not show an appreciable reticulocytosis until 14 weeks of life, and the Rh-negative infant, incorrectly selected, had a cord haemoglobin value of 140%, but the haemoglobin value in infant's cells was only 70%.

Three infants died. The cord haemoglobin values were 18%, 21%, and 26%. Cardiac arrest at the start of a second exchange transfusion was responsible in one case, pulmonary haemorrhage at 18 hours in another, and pulmonary haemorrhage and kernicterus on the fourth day in the third infant.

All surviving infants have been followed up at three-monthly intervals. At the time of writing the eldest was 18 months and the youngest 5 months. Developmental milestones, weight gain, and physical examination were normal in all but two. These exceptions are:

(1) An infant with severe haemolytic disease, heart failure, thrombocytopenia, and mild respiratory distress who was noticed to have a patent ductus arteriosus. At 6 months the ductus was still patent, and, though developmentally and physically normal, he was underweight.

(2) An infant with a cord haemoglobin of 38% with no donor cells demonstrable at birth suffered very severe respiratory distress, requiring 90% oxygen for 12 days with dextrose and intravenous nikethamide. At 1 year he was somewhat retarded and there was radiological evidence suggesting cerebral atrophy.

Congenital abnormalities were not a feature as in some reported series (Charles *et al.*, 1966). The only congenital defects observed, apart from the patent ductus, were two cases of squint. There have been no cases of deafness, even on audiometric examination, and there was no increase in the incidence of infection (Gordon *et al.*, 1966). Apart from the partial intestinal obstruction and partial femoral artery occlusion mentioned earlier, no complications in this series were attributable to the technique of intrauterine transfusion.

Discussion

Previous to any consideration of intrauterine transfusion it is well to remember that with conservative treatment 80% of all cases of Rh-isoimmunization will result in a living infant. In first affected pregnancies 90% will result in surviving infants.

Stillbirth occurs in 15% of cases overall and 50% of the stillbirths occur before 35 weeks' gestation. Those occurring late in pregnancy, if able to be identified, could be prevented by premature induction, but for those occurring early in pregnancy only intrauterine transfusion offers some prospect of help. The difficulties and dangers of the procedure, however, call for the most accurate possible selection of patients. In all published series the final selection has been based on liquor examination, but this necessitates amniocentesis, which is potentially dangerous. The majority of patients in whom early intrauterine death occurs are in the 10% of those who have a history of previous stillbirth or very severe disease. For these patients we recommend amniocentesis as early as 20 weeks' gestation. This is repeated, with or without intrauterine transfusion, at intervals of two to three weeks throughout pregnancy.

It should be remembered that the neonatal mortality in infants with severe haemolytic disease induced at 32 weeks is as high as 40%, compared with 20% in those induced at 35 weeks and 2% at term. Practically, intrauterine transfusion has done away with the need to carry out premature induction at 32 weeks, but though theoretically it should obviate entirely the need for premature induction in Rh-isoimmunization most workers still prefer, in the present state of knowledge, to induce labour when they think that the risks of prematurity are no longer overwhelming.

A second group of patients suitable for intrauterine transfusion can also be identified. We advocate amniocentesis at 32 weeks when a previous infant has been severely enough affected as to require any form of treatment. In this second group only one intrauterine transfusion should be needed. Subsequent refinements may select a small proportion of this group where amniocentesis earlier in pregnancy could be justified.

Because liquor bilirubin levels fall as pregnancy advances and because levels can be quite high at early stages of gestation even in normal pregnancy, very careful interpretation of the liquor results is necessary and there is need for accurate assessment of the stage of gestation (Walker, 1967). Our present criteria of bilirubin levels in liquor appear to be relatively satisfactory. We now carry out "early" intrauterine transfusion only if two consecutive values are higher than 1.1 and preferably showing a rise. However, in cases where the initial amniocentesis is made at 32 weeks intrauterine transfusion is performed if the ratio at that time exceeds 1.1.

The difficulties of the technique of intrauterine transfusion and the accidents that can occur have been covered in this report, but some points require special emphasis. We believe that the amount of blood injected, particularly into a small foetus, is important. Theoretically, exchange transfusion in utero (Adamsons, 1966) should be safer, but the greater dangers involved must restrict its use, and its contribution to the problem of intrauterine death can only be minimal. Liley (1964) originally regarded the presence of ascites as a contraindication to intrauterine transfusion, but 12 of our survivors had ascites removed on at least one occasion and Bowman (1966) has also reported survival in similar circumstances. It is desirable to avoid injecting large numbers of lymphocytes at intrauterine transfusion, for it appears that immunologically competent lymphocytes may occasionally colonize the reticuloendothelial system and produce complications (Cohen *et al.*, 1965 ; Kadowaki *et al.*, 1965 ; Githens, 1966 ; Naiman *et al.*, 1966).

Of course the later in pregnancy that patients are selected for intrauterine transfusion the better the results will appear ; for not only is the operation technically more simple at later gestations but many of the very severe cases where intrauterine transfusion is especially applicable will already have resulted in stillbirth. In our 1966 series 21 cases initially treated before 30 weeks' gestation resulted in 11 stillbirths and 10 live births, whereas all seven treated after 30 weeks' resulted in live births. This point should be considered when evaluating published series.

In Table III we have summarized the three large English series. Though overall the survival rates were similar, the first point of difference is the time at which the initial intrauterine transfusion was carried out. Thus 75% of Newcastle cases were treated before 30 weeks' gestation, compared with 60%

TABLE III.—*Time of Intrauterine Transfusion and Survival in Three Reported English Series*

Gestation at First I.U.T.	Karnicki and Holman (1966) Lewisham		Gordon *et al.* (1966) Hammersmith		Present Series. Newcastle, 1966	
	Total	Survived	Total	Survived	Total	Survived
Before 30 weeks ..	19	3 (15·8%)	12	4 (33·3%)	21	9 (42·9%)
After 30 „ ..	35	24 (68·6%)	8	6 (75%)	7	6 (85·7%)
All cases ..	54	27 (50%)	20	10 (50%)	28	15 (53·6%)

of Hammersmith cases and only 35% in the Lewisham series. The survival rate with these early transfusions was 43% in the Newcastle cases, 33% in the Hammersmith cases, and 16% in the Lewisham cases, but in each of the series the mortality rate was much higher in those cases treated before 30 weeks' gestation than in those treated later (with 70–85% survival).

Another point of difference was the onset of premature labour after intrauterine transfusion. This occurred within nine days of operation in 4% of the Newcastle cases, in 24% of the Lewisham cases, but in 65% of the Hammersmith cases. The reason for the difference is unknown but may be related to trauma or to leaving the catheter in situ between transfusions. Obviously if labour occurs early in pregnancy survival is jeopardized, and if later it is doubtful whether the foetus can have benefited significantly from the intrauterine transfusion. Indeed if large quantities of donor blood are still present in the peritoneal cavity after birth, continued absorption may contribute to the development of hyperbilirubinaemia (Fong, 1966).

Allowing for the severity of haemolytic disease and the degree of prematurity in the infants after intrauterine transfusion, we have not found particular problems in management except in one respect. The reticulocyte count on cord blood is often much lower than one would expect in relation to the haemoglobin level, and this erythroid hypoplasia persists longer and simple transfusion is required more often. Long-term follow-up, however, does not suggest any permanent defect. The leucocyte and platelet counts were not abnormal though increases in certain immunoglobulins have been noted (to be published). In the follow up of these cases, however, there has proved to be no difference in infection rates.

Though some of the deaths occurring immediately after intrauterine transfusion may have been due to technical difficulties, and certainly such cases have been recorded (Gordon *et al.*, 1966), no permanent sequelae have resulted in our surviving infants.

As regards neonatal death after intrauterine transfusion, we find that 3 out of 20 (15%) in Newcastle died, compared with 6 out of 16 (37%) at Hammersmith and 9 out of 36 (25%) at Lewisham. Perhaps comparisons of later series will produce more equitable results, but meanwhile the combined English series compares favourably with results from series in the rest of the world—up to February 1967 291 patients receiving 507 intrauterine transfusions with 118 (41%) infants surviving.

Provided that it is recognized that this procedure is not the panacea to prevent all Rh-stillbirths and that there is still difficulty in selecting the most suitable cases, there seems little doubt that, in spite of its hazards, intrauterine transfusion has a select and important part to play in the management of some cases of Rh-haemolytic disease of the newborn

> "diseases desperate grown
> By desperate appliance are reliev'd,
> Or not at all."—*Hamlet*, IV, iii, 9.

Summary

The criteria for selection of patients for intrauterine transfusion are discussed and experience with the procedure in 1965 and 1966 in the Newcastle upon Tyne hospitals is presented. Thirty-five foetuses received a total of 77 intrauterine transfusions, and 19 were born alive; 16 survived. It is concluded that in spite of the hazards intrauterine transfusion has a select and important part to play in the management of some cases of Rh-haemolytic disease.

We would like to thank our obstetric colleagues in the area who kindly referred patients to us. We would also like to record our appreciation of the considerable part played in this work by medical and nursing staffs of the Princess Mary Maternity Hospital and the Newcastle General Hospital, the staffs of the radiological departments at Newcastle General Hospital and the Royal Victoria Infirmary, and the staffs of the Regional Blood Transfusion Service and the Attic Laboratory. Without the co-operation of this team of people the studies described could not have been undertaken.

References

Adamsons, K., jun. (1966). In *Intrauterine Transfusion and Erythroblastosis Fetalis*, Report of Fifty-third Ross Conference on Paediatric Research, edited by J. F. Lucey and L. J. Butterfield, p. 71.

Bowman, J. M. (1966). Ibid., pp. 101, 103.

Charles, A. G., Alpern, W. M., and Friedman, E. A. (1966). *Obstet. and Gynec.*, **28**, 182.

Cohen, F., Zuelzer, W. W., Kadowaki, J., Thompson, R., and Kennedy, D. (1965). *J. Pediat.*, **67**, 937.

Fong, S. W. (1966). In *Intrauterine Transfusion and Erythroblastosis Fetalis*, Report of Fifty-third Ross Conference on Paediatric Research, edited by J. F. Lucey and L. J. Butterfield, p. 108.

Githens, J. H. (1966). Ibid., p. 104.

Gordon, H., Grausz, J. P., Raphael, M., and McClure Browne, J. C. (1966). *J. Obstet. Gynaec. Brit. Cwlth*, **73**, 917.

Kadowaki, J., Thompson, R. I., Zuelzer, W. W., Woolley, P. V., Brough, A. J., and Gruber D. (1965). *Lancet*, **2**, 1152.

Karnicki, J., and Holman, C. A. (1966). *Postgrad. med. J.*, **42**, 755.

Kleihauer, E., Braun, H., and Betke, K. (1957). *Klin. Wschr.*, **35**, 637.

Knox, E. G., Fairweather, D. V. I., and Walker, W. (1965). *Clin. Sci.*, **28**, 147.

Liggins, G. C. (1966). *Obstet. and Gynec.*, **27**, 617.

Liley, A. W. (1963). *Brit. med. J.*, **2**, 1107.

—— (1964). *Aust. N.Z. J. Obstet. Gynaec.*, **4**, 145.

—— (1965). *Pediatrics*, **35**, 836.

Naiman, J. L., Punnett, H. H., Destiné, M. L., and Lischner, H. W. (1966). *Lancet*, **2**, 590.

Savage, R. D., Walker, W., Fairweather, D. V. I., and Knox, E. G. (1966). Ibid., **2**, 816.

Walker, W. (1960). In *Proceedings of Seventh Congress of European Society of Haematology, London, 1959*, edited by E. Neumark, Part II, p. 1186. Basel.

—— (1967). *Brit. med. J.*, **2**, 840.

Work, B., Jaffe, R. B., Campbell, C., and Whitehouse, W. (1966). *Obstet. and Gynec.*, **27**, 319.