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EXCHANGE TRANSFUSION IN HAEMOLYTIC DISEASE OF THE NEWBORN

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PART I. TREATMENT

In the treatment of haemolytic disease of the newborn we regard it as proved that early exchange transfusion is superior to simple transfusion. The evidence in support of this was obtained in controlled trials carried out in various British centres between October, 1949, and August, 1951 (Mollison and Walker, 1952).

The Newcastle-upon-Tyne cases that formed part of these trials provide a comparison between early exchange and late simple transfusion. All infants in this centre were the result of spontaneous delivery. Those with a cord Hb level of 14.8 g. % or less were selected at random for either exchange or simple transfusion. When indicated, exchange transfusion of at least 60 ml. per lb. (132 ml. per kg.) body weight was carried out within nine hours of birth. A total of 86 children were included in the trial (Table I). In the group selected for simple transfusion this was given if the Hb level fell to 11 g. % during the first fourteen days of life. Apart from the type of transfusion given, all babies received identical care.

TABLE I.—*A Controlled Trial of Exchange and Simple Transfusion in 86 Infants with Haemolytic Disease (National Investigation, Newcastle-upon-Tyne Centre, 1949–52)*

	No. of Cases	No. with Kernicterus	No. of Deaths
Simple transfusion ..	42	9	13
Exchange „ ..	44	0	2

Of the 42 babies treated by simple transfusion, 13 died, whereas of the 44 treated by exchange transfusion only two died. Nine of the 42 treated by simple transfusion developed kernicterus, whereas no baby in the exchange transfusion group did so. The probability of such differences being due to chance is about 1 in 1,000.

Five infants had birth weights of 5½ lb. (2.5 kg.) or less. By chance, all were treated by simple transfusion and four died with kernicterus. We have calculated the probabilities after excluding these cases. The findings are still significantly in favour of exchange transfusion, but of course to a less degree. In relation to both mortality and kernicterus *P* now equals 0.02–0.01.

The purpose of this communication is to describe our experience of 250 consecutive cases treated by adequate exchange transfusion between March, 1947, and March, 1954. The evaluation of the procedure depends on various factors, while its effectiveness is closely related to details of technique. Our experience will therefore

be presented in two parts—the first dealing with indications and results, and the second with technique. We are concerned essentially with the application of our collected observations to daily practice.

Principles

From the start we felt that exchange transfusion was indicated and justified only in the more severely affected cases of haemolytic disease of the newborn, and throughout have tried to confine it to infants in whom there was a real risk of death or in whom transfusion was almost certain to be required sooner or later.

It has been our practice to use partly packed “bank” blood from either sex, and all but one of our 250 adequate exchange transfusions have been performed by the umbilical route, as will be described in Part II.

We have aimed to carry out, within the first nine hours of life, an exchange of 80 ml. per lb. (176 ml. per kg.) body weight. This amount was decided upon because it is equivalent to at least two blood volumes, and Wiener and Wexler (1946) had calculated that this gave 85% exchange, while the use of 120 ml. per lb. (264 ml. per kg.) raises the degree of exchange only by a further 8%. The period of nine hours was chosen because it was one of the rules governing the national trials, and we found that it was a convenient time limit and gave good results. Sometimes, for one reason or another, it is not possible to complete the full 80 ml. per lb. (176 ml. per kg.) and we have accepted as “adequate” any transfusion resulting in the exchange of 60 ml. per lb. (132 ml. per kg.), as again this was one of the rules governing the national trials. Anything less than 60 ml. per lb. (132 ml. per kg.) has been classed as “inadequate.” Obviously the nine-hour time limit can only apply to infants seen at or shortly after birth, but we have performed exchange transfusion on many infants seen later than this, and in such cases have begun treatment as early as possible. The effectiveness of exchange transfusion must depend to some extent on the volume of blood exchanged and the age at which it is carried out. We have not made a special point of trying to assess these factors, and any observations that we have made concerning them are incidental.

Material

The material on which this report is based is derived from 272 cases* selected for exchange transfusion between March, 1947, and March, 1954. In 1947 and 1948 only eight adequate exchanges were performed, while 19 were inadequate. During the next five years there have been 242 adequate transfusions and only three inadequate—two in 1949 and

*Cases from the Princess Mary Maternity Hospital, General Hospital, and Babies' Hospital, Newcastle-upon-Tyne, and the Queen Elizabeth Hospital, Gateshead, and a small number treated by us in other hospitals outside this area.

one in 1951. This is a reflection of the increasing experience with the technique and improvement in preparation and maintenance of equipment.

Premature induction has never formed part of our routine practice, but recently we have performed induction in cases in which there was a history of a previous stillbirth due to haemolytic disease and in which the father was homozygous Rh positive. Our experience of this type of case is limited to 10, so it is obviously much too early to draw conclusions from the results. Four of the resulting infants were treated by exchange transfusion and are included in this series. Any other premature infants in this series were the result of spontaneous premature labour or a pregnancy terminated prematurely for some independent obstetrical indication.

Indications For Exchange Transfusion

We have relied on certain criteria of severity to decide if treatment was required in a particular case, and in the light of experience have found it necessary to change these criteria on two occasions.

Our indications for exchange transfusion have been as follows, and they apply both for mature and for premature infants.

1. March, 1947, to September, 1949

(a) Any first affected infant showing jaundice or other clinical signs of disease within eight hours of birth. (b) Any subsequent affected infants showing clinical evidence of disease within the first twenty-four hours. These criteria were helpful, but depended on signs which could be difficult to assess and missed some cases that developed kernicterus, while perhaps 20% were treated unnecessarily.

2. October, 1949, to August, 1951

This was the period of the national trials, and the criterion used was a cord Hb value of 14.8 g.% or less. Eighty-six cases fulfilled this condition, but only 44 received exchange transfusion; the remaining 42 selected at random served as controls and received simple transfusion only for the treatment of severe anaemia.

The level of 14.8 g.% proved satisfactory in that only 4 of the 42 control cases did not require treatment. All four had levels between 13.2 and 14.8 g.%. As the other 11 cases in this range required treatment, we felt justified in retaining the criterion of 14.8 g.%, considering it advisable to allow for error in Hb determination, even if erring on the side of overtreatment. Moreover, 14.8 g.% corresponds with the lower limit of cord Hb in the majority of normal infants.

Ninety-five other infants with cord Hb values greater than 14.8 g.% were born during this period. None received early treatment. Twenty-three had cord Hb levels higher than 17.7 g.%. None died; indeed, only one required transfusion. We therefore felt it safe to leave untreated any infant with a cord Hb level greater than 17.7 g.%.

We were disturbed, however, to find that of 72 infants with cord Hb values between 14.8 and 17.7 g.%, five developed kernicterus, while 16 others eventually required transfusion for the relief of anaemia. One infant with a cord Hb level of 17.5 g.% died with kernicterus, while the Hb values in infants requiring transfusion were evenly distributed throughout this range—that is, 5 out of 20 with cord Hb values between 14.8 and 15.5 g.% and 16 out of 52 with values between 15.5 and 17.7 g.% required treatment. We therefore felt that the criterion of cord Hb alone was not satisfactory, because if the level was set high enough to include all infants at risk it would mean subjecting a large number to unnecessary treatment.

Between the levels of 14.8 and 17.7 g.% some different means of selecting cases for treatment was therefore required. It was in this respect that the cord bilirubin level promised to be of value. We had made cord bilirubin estimations on 52 infants in this range. The lowest level associated with the development of kernicterus was 2.8 mg. per 100 ml. In

fact, 13 infants had cord bilirubin levels of 2.8 mg. per 100 ml. or more, and three of these developed kernicterus, while five others required transfusions. In contrast, only 4 out of 40 infants with cord bilirubin levels of less than 2.8 mg. per 100 ml. required treatment. There were no deaths in this group and none required treatment in the first two weeks of life.

We therefore decided to adopt new criteria for exchange transfusion, and, as relatively few cases would be involved, considered that a controlled trial was not advisable: rather, we would judge their value by dealing with the prevention of kernicterus and the proportion of cases surviving without treatment.

3. September, 1951, to March, 1954

The criteria, still based on cord blood examination, were extended to include any infant with a cord Hb level of 14.8 g.% or less and any infants with cord Hb level between 14.8 and 17.7 g.% associated with a cord bilirubin level of 2.8 mg. per 100 ml. or more.

Since adopting these criteria, we have not seen a single case of kernicterus in a baby with less severe disease than they define. We cannot, of course, say accurately how many babies have been treated unnecessarily, but there has certainly been no mortality among the babies treated because of a high bilirubin level.

In this period we obtained cord blood samples suitable for both Hb and bilirubin estimation from 264 live-born infants with haemolytic disease of the newborn: 162 (61%) met the above criteria for exchange transfusion. A further seven infants were eventually transfused because of anaemia. No infant left without exchange transfusion died, and none required transfusion within the first three weeks of life. Altogether, 95 (36%) survived without any treatment at all. This corresponds closely with the expected proportion not requiring treatment. In a local series (Walker, 1950) collected between 1947 and 1949, when exchange transfusion was being used in only a minority of cases, 42% survived without treatment, while during the period of the national trials 43% survived without treatment.

Present Indications For Exchange Transfusion When Full Cord Blood Results Are Not Available

In cases in which for any reason the cord Hb or bilirubin level alone was available, this has been used as a guide in assessing the severity of disease. Nine infants with bilirubin levels higher than 2.7 mg. per 100 ml., but whose cord Hb was not known, were born at home and seen too late to be treated by exchange transfusion. Two died with kernicterus, three required simple transfusion, while the other four survived without treatment.

When neither cord Hb nor bilirubin estimations were available we have regarded the onset of clinical disease in the first eight hours of life as an indication for exchange transfusion, provided that evidence of brain damage was not already manifest when the infant was first seen.

In infants in whom neither the cord blood results nor the accurate information regarding the early clinical picture were available, Hb and bilirubin estimations on venous blood assisted in assessing the severity of the disease.

Indications For Repeated Exchange Transfusion

Unfortunately, early adequate exchange transfusion does not guarantee that kernicterus will be prevented. The known association of kernicterus and deep jaundice has consequently led to repeated exchange transfusions being recommended "in infants with severe and rapidly increasing jaundice, or if the bilirubin is more than 20 mg. per 100 ml. or likely to go that high." Using these criteria, Diamond *et al.* (1952) found it necessary to do multiple exchange transfusions in 20% of their cases.

In our experience kernicterus has occurred in only 2 out of 196 mature infants but in 3 out of 22 premature infants

treated by early adequate exchange transfusion. This disproportionate risk between mature and premature infants corresponds with our observation that after exchange transfusion 45% of premature infants developed deep jaundice; whereas only 13% of mature infants did so. We therefore feel that repeated exchange transfusion should be necessary only in a very small proportion of cases, and these mainly premature infants. The bilirubin level during the first week of life will probably prove the most satisfactory criterion for selecting cases for repeated exchange transfusion, and we have provisionally taken 25 mg. per 100 ml. as our indication.

Up to March, 1954, we had performed repeated exchange transfusion in only four infants. Three were born at labour induced surgically because of a previous history of stillbirth due to haemolytic disease of the newborn and because the father was homozygous Rh positive.

The fourth, a mature infant, was transfused with blood that, in retrospect, we thought had been overheated. The baby became deeply jaundiced and developed haemoglobinuria the day following exchange transfusion. As intense intravascular haemolysis was occurring, we decided to perform a second exchange transfusion. The response was dramatic; the bilirubin fell from 32.5 to 12.6 mg. per 100 ml. during the procedure. Haemoglobinaemia disappeared immediately and no subsequent haemoglobinuria occurred. Eighteen hours after the second exchange transfusion the bilirubin was 16 mg. per 100 ml., but fell thereafter, and jaundice had practically disappeared three days after the second transfusion.

Altogether in 1954 eight premature infants were treated by exchange transfusion, and two of these required a further exchange transfusion, whereas only 5 of 79 mature infants treated by exchange transfusion required further exchange. It should be pointed out, however, that two of these five were the result of premature induction at 35 weeks' gestation, while a third was first treated at the age of 4 days when the bilirubin level was 60 mg. per 100 ml.

Age at Time of Exchange Transfusion

It has always been our aim to start exchange transfusion within the first nine hours of life, but in 28 cases transfusion was not started until later, usually because the baby was born at home with resultant unavoidable delay. One such case, a mature baby, received an exchange transfusion of 80 ml. per lb. (176 ml. per kg.) at the age of 19 hours, but subsequently died from pulmonary haemorrhage and kernicterus. Of the 222 treated within nine hours of birth, 196 were mature* infants, and only two of these developed kernicterus.

Wallerstein (1947) recorded four deaths due to kernicterus among 27 cases treated by exchange transfusion. All four were treated later than twenty-four hours, when jaundice was already well marked.

We regard it as convenient and satisfactory to start exchange transfusion within the first nine hours of life in infants born in hospital and diagnosed by means of tests on cord blood. We have formed the strong impression that the general condition of infants with haemolytic disease improves during the first few hours of life—as might be expected from experience of the normal baby. If delivery has been difficult, or if the infant's condition is poor for reasons other than haemolytic disease, this preliminary period of acclimatization is all the more important, and oxygen therapy may be helpful. After nine hours we have observed a tendency for the general condition to deteriorate, and in particular a number of babies in good condition at birth were very ill by the time they were admitted to hospital for treatment.

On the other hand, immediate treatment may be called for, as in six cases in which we started the transfusion within the first hour of life. Each infant was desperately ill at birth, with a Hb level less than 6 g.% and signs of

heart failure. None had shown any improvement in the short interval before treatment started. Three survived, and the clinical improvement during the transfusion was most dramatic. The other three died during the transfusion, and two of these were found at necropsy to be hydropic.

Within these limits we feel that the actual time for exchange transfusion can be decided by convenience and by clinical observation of the individual baby, and prefer, as a rule, to begin treatment at about four to six hours.

Volume of Blood Exchanged

As stated previously, we have always aimed to exchange 80 ml. per lb. (176 ml. per kg.) body weight, or twice the baby's estimated blood volume. This accords with the recommendations of various workers (Wiener and Wexler, 1946; Wallerstein, 1947; Diamond *et al.*, 1952), and should result in about 85% of the baby's blood being replaced by donor blood. The blood required, except in babies weighing more than 8½ lb. (3.9 kg.), can be obtained from two bottles of partly packed "bank" blood. We have not varied the volume of blood exchanged in relation to the cell volume of infant and donor blood, as suggested by Veall and Mollison (1950); therefore, there has been a relatively greater degree of replacement in the more anaemic cases, and this seems to us to be an advantage. The application of Veall and Mollison's nomogram will, however, enable adequate exchange transfusion to be carried out with minimal quantities of blood. Wiener and Wexler (1949) suggested that in very severely affected infants as much as 1,000 ml. should be exchanged, but it seems to us that the slight increase in the completeness of exchange so achieved is offset by the risks of the longer procedure. Indeed, the same authors (1951) later suggested that an exchange of 100–150 ml. of packed red cells was adequate. It is well to remember that as the exchange transfusion progresses, so the relative effectiveness of each 10 ml. of blood exchanged diminishes. Therefore, if the infant's condition gives cause for anxiety towards the end of transfusion it may be wiser to stop, rather than to carry on in an effort to reach the target figure.

Our secondary aim in performing exchange transfusion has been to achieve a final Hb level of between 15 and 17 g.%. This reduces the possibility of further transfusion being required, but, more important, it depresses erythropoiesis and the production of cells liable to rapid haemolysis.

We have made no systematic observations on the relationship between percentage exchange and mortality, but in the period 1947–9, 20 cases selected because of early clinical disease received inadequate exchange transfusions. Seven of the 20 receiving inadequate exchange transfusions died, while 18 of the 51 treated by simple transfusion died—that is, a mortality rate of 35% in each group. Three cases of kernicterus occurred in the exchange and 11 in the simple transfusion groups. It seems, therefore, that exchange transfusion of less than 60 ml. per lb. (132 ml. per kg.) gives no better result than simple transfusion.

Davies *et al.* (1953) claimed that, in their experience, an exchange of 60 ml. per lb. (132 ml. per kg.) did not prevent kernicterus; whereas 80–100 ml. per lb. (176–220 ml. per kg.) exchange or two exchanges each of 60 ml. per lb. (132 ml. per kg.) did so.

Mortality in Cases Treated by Exchange Transfusion

Even accepting that adequate exchange transfusion is superior to simple transfusion, we still require to assess the part it may be expected to play in the management of haemolytic disease. Can exchange transfusion be recommended as a safe routine procedure? Are there special risks associated with the method itself? Are there some cases in which exchange transfusion is ineffective? If adopted as the treatment of choice for all cases likely to require treatment, what order of improvement in survival can be expected?

Although the results of many series of cases treated by exchange transfusion have been published (Hart, 1925;

*Weighing more than 5½ lb. (2.5 kg.) at birth.

Wallerstein, 1946, 1947, 1948; Wiener and Wexler, 1946, 1949; Diamond, 1947, 1948; Mollison and Cutbush, 1948; Diamond *et al.*, 1952), the answers to these questions are not readily found. The reason is that many of the series are small and highly selected, so that they do not represent the disease as a whole, nor is one series necessarily comparable with another.

Certain earlier reports cannot be accepted at their face value, because standards of diagnosis were changing as well as methods of treatment. The pitfalls of these interpretations are illustrated by Diamond (1947), who reported reduction in mortality with changes in treatment, as follows:

Period	Treatment	Mortality
Pre-1941	Simple transfusion (probably Rh positive)	40%
1942-4	(Rh negative)	30%
1944-6	Premature induction and simple transfusion (Rh negative)	20%
1947-	Premature induction and exchange transfusion (severe cases excluded)	10%

It seems possible that the reduction in overall mortality was not due solely to improvement in treatment, but could, in part, be explained by improvement in diagnosis. Before 1941, when the diagnosis was made on clinical grounds, only severe cases, mainly those presenting the clinical picture of icterus gravis, would be included. With the increasing use of serological methods of diagnosis one would expect an increasing proportion of the recognized cases to be mildly affected, with a corresponding reduction in mortality irrespective of improvements in treatment. In confirmation of this hypothesis, we found, during a survey of cases in the Northern Region for 1947-9 (Walker, 1950) that there was a mortality rate of 40% in cases diagnosed clinically as icterus gravis, but of only 15% in the group as a whole, which included cases diagnosed on serological evidence alone.

The published series vary in size from 9 to 208 cases and the mortality rate from 6 to 32%. Many are too small to allow evaluation of the results, while in most the indications for exchange transfusion are so numerous and varied that they allow considerable freedom of interpretation and consequent intrusion of personal bias.

More recently, other factors—for example, the use of female blood and the performance of multiple exchange transfusion—have been reported as bringing about a fall in mortality.

Results

The following are our results in all cases in which exchange transfusion of at least 60 ml. per lb. (132 ml. per kg.) was carried out.

In the past five years only 3 out of 245 infants selected for exchange transfusion have not received a transfusion of at least 60 ml. per lb. (132 ml. per kg.). Two were technical failures, while the third, born *in extremis*, died before the transfusion could be completed. It is known that premature infants are at greater risk than mature babies, and we think that infants born in hospitals offering special facilities stand a better chance than infants admitted from "outside"; we therefore present our results in three groups. No case has been omitted, and none has been included in more than one group.

Group I.—Premature Infants. All infants with birth weights of 5½ lb. (2.5 kg.) or less are included. As there are so few cases in this group, we have not subdivided them in relation to the means by which they were selected for exchange transfusion, nor by the age at which this was carried out.

Group II.—Mature infants born at home, or in hospitals not affording special facilities. These cases were selected for treatment usually because of the early appearance of clinical disease as already defined, or, in some more recent cases, because the cord blood specimen taken routinely from the infants of all Rh-negative mothers was found to be Coombs-positive and to have a bilirubin level of 2.8 mg. per 100 ml. or more. Many were not treated until after the age of nine hours.

Group III.—Mature infants born in hospitals affording special facilities, selected on the basis of cord Hb and bilirubin levels and treated within nine hours of birth. This group includes all the national trial cases.

In Table II we have classified deaths as due to haemolytic disease or to other causes. It is realized that when death occurs in a baby suffering from haemolytic disease of the newborn one can never be absolutely certain that this disease played no part in causing death. Post-mortem examinations were made in all fatal cases, and the cause of death recorded is that given by the pathologist.

The causes of death are shown in Tables III and IV, and brief clinical notes on these cases are included in an Appendix.

None of these infants had evidence of kernicterus at necropsy. All but the first and last cases were very ill at the time of transfusion, and in them the diagnosis eventually recorded as the cause of death was made before treatment was started.

TABLE II.—Results in 250 Cases of Haemolytic Disease of the Newborn Treated by Adequate Exchange Transfusion

Group	No. of Cases	Neonatal Deaths		Mortality Due H.D.N.	Kernicterus
		Due to H.D.N.	Other Causes		
I	22*	6	2	27%	2 died (A and WK) 1 survived (Mu)
II	37	4	3	11%	1 died (G)
III	191	5	3	2.6%	1 survived (F)
Total	250	15	8	6%	5

* 3 multiple exchange transfusions.

TABLE III.—Deaths Not Attributed to Haemolytic Disease of the Newborn

Group I	Cerebral haemorrhage	H
"	" birth injury	McA
II	Pneumonia	Th
"	Cerebral birth injury	T
"	Subdural haematoma	A
III	Atelectasis	K
"	Vernix inhalation	P
"	Overlaid	F

TABLE IV.—Deaths (15) Attributed to Haemolytic Disease of the Newborn

Group	Hydrops Foetalis	Kern-icterus	Heart Failure	Generalized Bleeding	Cardiac Arrest	Cirrhosis of Liver	Not Known
I	2 (WI) (E)	2 (WK) (A)	1 (O'H)	—	1 (Be)	—	—
II	—	1 (G)	3 (DO) (D) (ATH)	—	—	—	—
III	—	—	1 (B)	2 (H) (Da)	—	1 (O)*	1 (L)
Total	2	3	5	2	1	1	1

* Died at 6 months with terminal respiratory infection. At necropsy, cytomegalic inclusion bodies were found. In the absence of proof to the contrary, this death has been attributed to haemolytic disease. No abnormality of the central nervous system could be demonstrated histologically.

Severity of Disease

The severity of disease in any particular series may differ from that in another, and this will obviously influence the results. The distribution of the factors most likely to influence the results—birth weight (Fig. 1), cord Hb (Fig. 2), and sex of baby—are shown, to serve as a means of comparison with other series.

Follow-up

First Six Weeks.—All infants were kept under observation during the first six weeks, and during this period 28 out of 229 (12%) required "topping-up" transfusion because the capillary haemoglobin level fell to less than 8.5 g.%. In 10 of these the explanation was that the infants were very severely affected and therefore exchange transfusion was

completed at a negative balance. In the remainder we could find no particular reason for the development of anaemia, but none required secondary transfusion during the first three weeks of life. These findings are in contrast to those

FIG. 1.—Birth weight of 250 infants treated by exchange transfusion. Males, 128; female, 116. Weight was not recorded in three cases.

FIG. 2.—Severity of H.D.N. measured by cord Hb in 209 infants treated by exchange transfusion.

icterus, one a mature baby and one a premature infant (F and Mu) and a third was regarded as a probable case (McD.). Another infant was mentally defective, but was regarded as a primary ament, not due to haemolytic disease. The remainder were judged to be normal children.

(Since this paper was submitted the remaining 50 cases have been seen at the age of 6 months or more, and all are apparently normal.)

Later Follow-up.—Some of these infants form part of a group being followed up for a longer period, and the results will be published later.

Conclusions

Although various methods of treating haemolytic disease of the newborn have been suggested from time to time (Hardwick and Lloyd, 1941; Homburger, 1946; Kariher and Miller, 1947; Carter, 1949, 1951; Pickles, 1949), so far there is no means of preventing immunization in an Rh-negative woman, or of protecting an Rh-positive foetus against the action of antibodies, once formed. Exchange transfusion, first recommended by Hart (1925), has, however, proved of great value in treating affected infants.

Exchange transfusion is a safe routine procedure and is recommended as the treatment of choice for the 60% of liveborn affected infants requiring treatment.

In experienced hands exchange transfusion carries a very low operative risk, and this risk is practically confined to infants whose chance of survival would be very poor if treated by other means.

In our experience, premature infants have a significantly worse chance of survival than mature infants, owing mainly to the increased risk of kernicterus. Therefore, prematurity should be avoided whenever possible.

of Davies *et al.* (1953), who found "topping-up" transfusion necessary in 60% of cases.

Ten to Fourteen Months.—We have tried to see the first 200 cases at the age of about 1 year, in order to assess development by means of simple observations and questioning. All survivors attended for follow-up, except 10 who lived at a distance. The mothers of all 10 wrote telling us of the child's development. In any cases in which there was any question of abnormality the infant was seen by an independent paediatrician. Two infants were regarded as definite cases of kernicterus.

In areas where exchange transfusion is adopted as the treatment of choice for all cases likely to require treatment, a survival rate of 98% of all live-born affected infants can be expected. Confirmation of this claim is to be found from consideration of the two years 1952 and 1953 (Walker and Murray, 1954), during which 217 infants with haemolytic disease were born in the Newcastle hospitals: 15 were premature, 125 (58%) were treated by exchange transfusion, while five more (2%) required simple transfusion. Seven died, but only four of these deaths were regarded as due to haemolytic disease—a mortality rate of 2%.

We believe that cord Hb and bilirubin levels permit selection of practically all cases likely to require treatment, and consider that exchange transfusion of 80 ml. per lb. (176 ml. per kg.) body weight, carried out within nine hours of birth, is indicated in these cases.

APPENDIX: CASE SUMMARIES FOR FATAL CASES

Not Attributed to Haemolytic Disease of the Newborn

Group I

H.—B. wt. 5 lb. (2.3 kg.). Cord Hb 12.7 g.%. Cord bilirubin 3 mg. per 100 ml. Infant became ill on the fourth day and died. Mild jaundice (bilirubin 3.6 mg. per 100 ml.) at time of death. P.M.: Cerebral haemorrhage; no kernicterus.

McA.—B. wt. 3 lb. (1.4 kg.). Cord bilirubin 5.6 mg. per 100 ml. Normal respiration never established; cyanosed whenever removed from oxygen; died during exchange transfusion. P.M.: Cerebral birth injury, medullary herniation.

Group II

Th.—B. wt. 6 lb. 8 oz. (2.9 kg.). A sick child with moaning respiration, treated at 11 hours. Died at 18 hours. P.M.: Bilateral bronchopneumonia; sticky mucus in trachea; haemorrhagic exudate in pleural cavities.

T.—B. wt. 6 lb. 12 oz. (3.1 kg.). Difficult delivery with foetal distress. Died at 2 days. P.M.: Cerebral birth injury.

A.—B. wt. 8 lb. 12 oz. (4 kg.). Precipitate labour. Severe haemolytic disease and respiratory difficulty regarded as cerebral in origin. Died at 2 days. P.M.: Cerebral birth injury; large subdural haematoma.

Group III

K.—B. wt. 6 lb. 1 oz. (2.7 kg.). Cord Hb 8 g.%. Cord bilirubin 15 mg. per 100 ml. Died at 3 days. P.M.: Atelectasis; pneumonia; no evidence of kernicterus, heart failure, or haemorrhage.

P.—B. wt. 7 lb. (3.2 kg.). Cord Hb 8 g.%. Admitted with marked cyanosis and asphyxial haemorrhages. P.M.: Atelectasis.

F.—B. wt. 6 lb. 9 oz. (3 kg.). Cord Hb 16 g.%. Cord bilirubin 4.1 mg. per 100 ml. Overlaid one week after discharge aged 3 weeks.

Attributed to Haemolytic Disease of the Newborn

Group I

Wl.—B. wt. 3 lb. 3 oz. (1.4 kg.). Cord Hb 4.6 g.%. Cord bilirubin 2.7 mg. per 100 ml. Twin of classical hydrops foetalis. Died during exchange transfusion. P.M.: Hydrops foetalis.

E.—B. wt. 4 lb. 10 oz. (2.1 kg.). Hb 4.8 g.%. Cord bilirubin 6.5 mg. per 100 ml. Died at end of exchange transfusion. P.M.: Hydrops foetalis.

WK.—B. wt. 5 lb. 8 oz. (2.5 kg.). Cord bilirubin 4.1 mg. per 100 ml. Died at 4 days, when bilirubin was 30 mg. per 100 ml. P.M.: Kernicterus.

A.—B. wt. 5 lb. (2.3 kg.). Cord Hb 17 g.%. Cord bilirubin 7.4 mg. per 100 ml. Died, deeply jaundiced, at 63 hours. P.M.: Kernicterus.

O'H.—B. wt. 5 lb. 3 oz. (2.4 kg.). A very ill infant that died at end of exchange transfusion. P.M.: Heart failure.

Be.—B. wt. 5 lb. (2.3 kg.). Cord Hb 11 g.%. Cord bilirubin 4.8 mg. per 100 ml. An infant the result of premature induction at 35 weeks, because of previous history of stillbirth due to haemolytic disease of the newborn. Second exchange transfusion was performed at 47 hours and the infant died suddenly during the procedure. We regard this death as caused by cardiac arrest due to hyperpotassaemia. P.M.: Nothing abnormal detected. This case is described more fully in Part II.

Group II

G.—B. wt. 7 lb. 3 oz. (3.3 kg.). Exchange transfusion at 19 hours, when deeply jaundiced. Died at 48 hours with kernicterus and massive pulmonary haemorrhage.

Do.—B. wt. 7 lb. 6 oz. (3.3 kg.). Given additional 70 ml. of blood at end of exchange transfusion. P.M.: Heart failure and dilated right heart.

D.—B. wt. 7 lb. 1 oz. (3.2 kg.). A very ill baby treated immediately after delivery. Collapsed and died during transfusion. P.M.: ? Heart failure.

Ath.—B. wt. 7 lb. 2 oz. (3.2 kg.). Very ill on admission, suddenly collapsed and died during exchange transfusion. P.M.: Heart failure.

Group III

B.—B. wt. 8 lb. (3.6 kg.). Cord Hb 5.9 g.%. Cord bilirubin 11.5 mg. per 100 ml. A very ill baby that improved dramatically during exchange transfusion but suddenly, when the transfusion was almost completed, collapsed and died. P.M.: ? Heart failure.

H.—B. wt. 7 lb. 8 oz. (3.4 kg.). Cord Hb 10.3 g.%. Cord bilirubin 1.9 mg. per 100 ml. Deteriorated towards end of exchange transfusion. Was semicomatose, with moaning respiration for 12 hours; death occurred. Had been given prophylactic vitamin K. P.M.: Haemorrhage into abdomen, pleura, pericardium, cranium; umbilical vein intact; hepatic necrosis.

Da.—B. wt. 7 lb. 4 oz. (3.3 kg.). Cord Hb 5.7 g.%. Cord bilirubin 4.9 mg. per 100 ml. Given prophylactic vitamin K. Twenty-four hours after exchange transfusion had fit, and six hours later developed pulmonary haemorrhage and died. P.M.: Haemorrhage into lungs, adrenal, kidney, and stomach; liver necrosis.

O.—Cord Hb 4.5 g.%. Bilirubin 8 mg. per 100 ml. Progressive jaundice and hepatosplenomegaly. Died aged 6 months. P.M.: Cytomegalic inclusion disease.

L.—B. wt. 8 lb. 2 oz. (3.7 kg.). Cord Hb 14 g.%. Cord bilirubin 2.9 mg. per 100 ml. Sudden death fifty minutes after exchange transfusion. P.M.: Nothing abnormal detected.

PART II. TECHNIQUE

The results of exchange transfusion in cases of haemolytic disease of the newborn, presented as Part I of this article, have convinced us that early adequate exchange transfusion is the treatment of choice for all cases in which treatment is likely to be required. The primary justification of this conviction lies in the infant's greater chance of survival, but exchange transfusion also has the very real advantage that it will avoid the necessity for frequent haemoglobin estimations and perhaps multiple transfusions.

The successful application of the principles set out in Part I depends on the performance of a series of technical procedures. In the past seven years we have attempted exchange transfusion in 272 babies, and 250 of these have been technically satisfactory. Only 3 of the 22 failures have occurred in the last five years, and this we attribute to increased experience of the procedure and improved maintenance of apparatus.

We have tried to develop a simple straightforward technique and hope that a description of the method we use and the difficulties we have encountered may be of help to others concerned with the practical management of these cases.

General Routine Governing Treatment

1. The disease is predicted antenatally by serological tests, and delivery in a hospital providing special facilities for the care of these infants is advised.

2. The umbilical cord is clamped about 15 cm. from the abdominal wall as soon as possible after delivery. Using a dry syringe and No. 1 needle, the midwife or the doctor collects 10 ml. of blood from the umbilical vein on the maternal side of the clamp. Half of the blood is transferred to a plain tube for serological tests, and half into one containing dry anticoagulant for haematological estimations.

3. If exchange transfusion is indicated, according to the criteria described in Part I, a time within the first nine hours is selected, dependent on the baby's condition.

4. Exchange transfusion is performed by the umbilical route, aiming to achieve 80–90% replacement.

5. The baby is kept in the special nursery for sick babies for a few hours; then, if well enough, he is taken to his mother in the lying-in ward.

6. Haemoglobin estimation, using skin-prick blood, is performed next day and repeated as indicated until discharge from hospital (usually on the tenth day). All babies are seen for examination and haemoglobin estimation at the age of 1 month, and a few need a further test at 6 weeks. This routine is followed in the straightforward case whether the infant has received early exchange transfusion or has been left without early treatment. If the haemoglobin level falls to less than 8.5 g.% during the first six weeks of life a simple scalp-vein transfusion is given.

Blood For Exchange Transfusion

For a baby weighing 8½ lb. (3.9 kg.) or less, two M.R.C. bottles of "bank" blood are required, usually Rh negative and of the same ABO group as the baby.

Compatibility Tests.—Blood is selected on the basis of tests in saline and serial dilutions in albumin, and by the indirect Coombs technique; ideally, both the mother's and the baby's serum are used. When the mother's serum is not available, or in an emergency, Rh-negative blood is used without performing a full compatibility test. In such circumstances we consult the record card to ensure that there is nothing unusual about the maternal antibody.

Age of Blood.—We prefer to use blood no more than three or four days old, but, on occasion, have used blood as old as 20 days without apparent ill effect. That there are advantages in using relatively fresh blood was made clear to us recently. Baby Be, a 5-lb. (2.3-kg.) premature infant with a cord haemoglobin level of 11 g.%, was treated by exchange transfusion at the age of 2½ hours. In spite of this the bilirubin rose, and at 44 hours was 24.7 mg. per 100 ml. A second exchange transfusion was carried out and a bottle of blood from the hospital bank was used. When 230 ml. exchange had been completed the baby suddenly became cyanosed, with grunting respiration, and death occurred almost immediately. At 200 ml. exchange the baby had been very well and the venous pressure 5 cm. As he had tolerated the first exchange well, and as the only unusual feature was that the blood used for the second transfusion was 15 days old, we wondered whether there might be some biochemical explanation. We found that the serum potassium level in the infant at the start of transfusion was 20.8 mg. per 100 ml. and at the time of death 57 mg. per 100 ml. The level in the transfused plasma was 65 mg. per 100 ml., and we therefore attribute this death to cardiac arrest consequent on hyperpotassaemia. This danger has been pointed out by Miller *et al.* (1952).

Hb Content of Blood.—Having been collected into acid citrate dextrose (A.C.D.), bank blood is likely to have a haemoglobin content of only about 11.5 g.%. Therefore, in order to achieve a haemoglobin level of 17 g.% at the end of the transfusion, it is necessary: (a) to give the baby considerably more blood than is withdrawn, or (b) to adjust the haemoglobin content of the transfused blood to approximately 17 g.% by removing about 200 ml. of plasma from each bottle. This latter method has been our constant practice since the very early days, because we regard overloading of the infant's circulation as a very real danger. Mollison (1951) also recommends using concentrated blood, but Diamond *et al.* (1952) advocate the use of whole blood.

On isolated occasions, when suitable bank blood has not been available, we have called donors, and have preferred to collect the blood into heparin rather than A.C.D., thus minimizing the degree of dilution.

Sex of Donor.—Allen *et al.* (1949) drew attention to the possibility that the sex of the donor might influence the

efficacy of exchange transfusion. In their series of 208 cases, 42 infants received blood from female donors, while 137 received male blood. No deaths occurred in the group treated with female blood, whereas 27 (20%) of those treated with male blood died. They claim that this is a significant difference, and state that it cannot be accounted for on the ground that blood with a high cell volume (and therefore generally from male donors) was purposely used for the most severely affected cases. However, Sacks *et al.* (1950), in their series in which the total mortality was similar to that of Allen *et al.*, found that 12.5% of cases transfused with male blood died, as against 21.8% of those treated with female blood. This suggests that the preferential use of female blood is of doubtful value. It has not been our practice to have the donor blood "sexed" before use, but we have been able to trace the sex of the donors in 158 cases. Fifty-five received male blood, 54 female blood, and 49 blood from both male and female donors. The mortality was the same in the three groups. We have taken account of the donor's sex in 12 fatal cases and in 9 very severely affected infants who survived, but could find nothing to suggest that female blood is superior to male blood. It would therefore seem unnecessary to take account of the sex of the donor when selecting blood for exchange transfusion.

Apparatus For Exchange Transfusion

The following material is required: Cord ligatures; gauze swabs; two transfusion stands; oxygen apparatus; cruciate frame; hot-water bottles; three pairs of small artery forceps; one pair of large scissors; exchange transfusion set; "polythene" catheters of two sizes, internal bore 2 mm. and 1 mm.; two short cannulae to fit tightly within catheters (S.W.G. 10 and 18 respectively); blood for transfusion; blood-collecting bottle containing acid citrate dextrose for waste.

Polythene tubing in 8-in. (20-cm.) lengths is stored in a rubber-stoppered glass tube containing 1% cetrimide and after 24 to 48 hours is sterile and ready for use. The catheter tip is cut square because a pointed catheter is more likely to perforate the vein and produce a false passage. We have found side holes a disadvantage. In 247 of our 250 cases we used a catheter with a 2-mm. bore and a 0.75-mm. wall, especially extruded for us by Messrs. De La Rue. This catheter proved satisfactory even with infants

weighing as little as 3 lb. (1.4 kg.) at birth. In two of the three remaining cases only a catheter of 1 mm. bore and 0.25 mm. wall could be passed, while the third was transfused by another route.

Transfusion Set

Many pieces of apparatus for exchange transfusion have been described. Our experience is limited to two—one described by Henderson (1950) but modified to take the larger polythene tubing, and one made for us by Messrs. Baird and Tatlock. This latter set, which we use almost exclusively, is illustrated in Fig. 3. It is very simple, and with the catheter attached the dead space is only 0.5 ml. The essential component consists of two two-way taps machined in one block with large bore throughout, and since it is very light a single operator can use it for long periods, as in the case of two immediately consecutive transfusions. The present pattern is Sima-fitting and made so that a syringe locks on to one end and a cannula on to the other. The locking device is of the pin-slot type, and this sometimes gives rise to air leaks. Therefore we have had a Luer-lock apparatus* made that is otherwise similar to that illustrated. The apparatus is completed by fitting two standard transfusion "giving sets" to the side limbs, but the one intended for waste blood is assembled without either filter or drip-chamber.

We have found "Everett" syringes absolutely satisfactory and prefer the metal-and-glass to the all-glass variety. All-glass syringes tend to stick, because any blood leaking back along the plunger is exposed to the air intermittently and dries. As a lubricant for taps and syringe silicone fluid† is used.

The ease of the operation depends on the use of a large-bore catheter, and, employing 2-mm.-bore tubing, we have not found a Tuohy adapter necessary. In most cases the same apparatus is used from start to finish without having to disconnect the syringe or wash out any part.

Sterilization.—The apparatus, apart from the catheter, is sterilized by autoclaving and is kept constantly ready for use; the syringes and cannulae in glass tubes, the set and instruments in separate "cellophane" packages.

Route of Transfusion

We normally use the umbilical vein route introduced by Diamond (1948), and, with one exception, our successful experience is limited to this route. We have found it absolutely satisfactory. Wallerstein's (1946) fears that it would be feasible only if a decision regarding transfusion were made before birth have proved unfounded. We disagree with the opinion of Field and Hawkins (1951) that many cases are seen too late for the umbilical vein to be used and that, in any case, it is dangerous because of the manipulations required and the rapid rate of transfusion.

Other routes have been recommended from time to time. The original method (Hart, 1925), also used by Wallerstein (1947, 1948), was that of saphenous or arm vein infusion, combined with the withdrawal of blood from the jugular vein or fontanelle. In our earlier cases we tried this method, but found it technically difficult, and we were able to achieve a satisfactory exchange in only one of the six cases attempted. The method also appeared to involve undue risk of bleeding from the punctured vessels.

* We have practically no experience of the saphenous vein and radial artery technique originally used by Polayes and advocated by Wiener and his co-workers (1946, 1949).

No doubt anyone taking enough trouble to master a technique will in the end find it reliable, but the umbilical route, in addition to its technical simplicity, has the following very real advantages: (1) No artificial wound is made; (2) the balance between the volume of blood given and withdrawn can be maintained very accurately or varied at will; (3) venous pressure can readily be measured directly

FIG. 3.—Apparatus for exchange transfusion.

*Supplied by the Medical Supply Association Ltd., Edinburgh.
†DC 550 Midland Silicones, Ltd.

when a transparent catheter is used; and (4) no important artery is ligated, for, although Field and Hawkins (1951) claim that ligation of the radial artery does no harm, Wallerstein (1948) maintains that there is a risk of ischaemia.

Technique of Transfusion

1. The transfusion is carried out in a warm room, if possible with a temperature of 75 to 80° F. (23.9 to 26.7° C.). The blood is placed in water at 98° F. (36.7° C.) for about 15 minutes before use. The baby, wrapped in gamgee so that only the face and umbilical areas are exposed, is bandaged to the cruciate splint in such a way that no bandages cross the abdomen or chest. A hot-water bottle is placed on each side of the trunk and held in place by a blanket which also forms a hood round the head.

2. Everyone entering the room wears a mask. The operator scrubs up and puts on a sterile gown, while his assistant, usually a nurse, merely washes. She records the amounts of blood exchanged throughout the procedure and notes the time taken for each 100-ml. exchange. She attends to the baby as necessary, including the administration of oxygen if required, and changes the blood bottles when indicated.

3. The cord is swabbed with 1% cetrimide and the baby is covered with a sterile towel, in the centre of which is a small hole. The apparatus is assembled and the blood and waste bottles are suspended from the transfusion stands. By manipulating the taps, blood and A.C.D. in turn are allowed to fill the rubber tubing, thereby expelling all air, while the citrate washes out any blood from the taps.

4. The umbilical cord is divided no more than 2 cm. from the abdominal wall and the stump is brought up through the hole in the towel and packed round with sterile gauze. The vein is readily identified, as it has a larger lumen than the two arteries, which usually lie close together and, because of their thicker walls, tend to protrude from the cut surface. The vein wall is grasped with artery forceps at two points opposite to each other and the closed third forceps is used as a blunt dilator to dilate the vein to a point just beyond the skin margin. A catheter is then introduced gently about 8 to 10 cm. to a point where blood flows freely back along it. If difficulty is experienced at the junction of cord and skin, the cord is gently pulled down in the direction of the pubis and the catheter rotated backwards and forwards, when it will usually pass without difficulty.

5. A direct measurement of the venous pressure can be made by elevating the external part of the catheter and measuring the height of the blood column above the abdominal wall. The measurement can be regarded as satisfactory only if the baby is quiet and relaxed and there is free fluctuation of the blood with respiration. We regard a pressure of less than 10 cm. as normal, but Diamond *et al.* (1952) regard 6 cm. as the upper normal limit.

6. The metal cannula is now inserted into the polythene catheter, attached to the tap unit, and the transfusion begun. 10 ml. of blood is first withdrawn from the baby, and, after turning the appropriate tap, is ejected into the waste bottle. Then 10 ml. of donor blood is taken into the syringe via the other tap, and, with both taps once more in line, is slowly injected into the baby. This cycle is repeated as often as necessary to complete the transfusion, and we aim to take ten minutes for each 100 ml. exchanged. On occasions we have taken as little as six minutes for 100 ml. without apparent ill effect, but too rapid transfusion often distresses the baby. Some experienced workers recommend carrying out the exchange in 20-ml. amounts, but this increases the completeness of the replacement by barely 1%, and we feel that the smaller volume is safer.

From beginning to end the operation takes about 75 minutes, which agrees with the recommendations of Wallerstein (1947), and Diamond *et al.* (1952). It is appreciably shorter than the time recommended by Mollison (1951) and Field and Hawkins (1951).

Difficulties, especially in withdrawing blood, often occur, but can usually be overcome by altering the position of the catheter slightly. Once the best position is found, every effort should be made to keep the catheter absolutely still. Gentle traction on the cord sometimes overcomes difficulties, presumably by straightening out a kink, but we have the impression that excessive traction tends to cause vomiting. The surest way to stop the flow is to suck too hard.

Defects in the apparatus can readily be located by testing it after disconnecting from the catheter.

If desired, additional blood may be given at the end of the exchange, either by the syringe in 10-ml. amounts or by slow drip, the donor set being connected direct to the cannula for this purpose. Unless it is certain that the infant will tolerate additional blood, none should be given. If necessary, a simple transfusion given several days later will serve the same purpose with greater safety.

At the end of the operation the cord is ligated in the normal way if long enough. If not, a purse-string suture is used, or a ligature tied round the skin-covered portion of the cord and removed 24 hours later.

Technical Difficulties

Introducing the Polythene Catheter

Difficulty in inserting the catheter can usually be avoided by cutting the cord sufficiently short, so that the remaining vein is not tortuous. It is also important to be sure that the lumen has been entered, for it is easy to make false passages, either alongside the vein or between the coats of the vessel wall. If the catheter has been introduced 8 to 10 cm. and blood has failed to flow, it should be suspected that the catheter is not in the vein. If suction produces only a small amount of yellow fluid this is certain. The remedy is to cut the cord shorter, if necessary flush with the skin, and start again.

Very occasionally the umbilical vein runs an atypical course, and, if varying the line of approach does not succeed, a curved probe can be used to determine the exact path of the vein. In such circumstances the introducing cannula described by Diamond *et al.* (1952) should be of value.

On one occasion we could pass the catheter only about 5 cm. beyond the skin margin, and withdrawal of blood was very difficult. We therefore cut down on the vein above the umbilicus (as described by Pinkus, 1948) and, presumably because of the more direct approach, were able to manipulate the catheter past the obstruction.

If the cord has been tied off short or occluded near the skin margin by means of a metal clip, it should be cut off close to the skin, and no difficulty should be encountered.

In the small number of secondary exchange transfusions that we have performed we have found it satisfactory in most cases to divide the cord close to the skin margin by means of a scalpel. The vein is identified and the catheter introduced in the usual way. Where we have failed with this method we have cut down on the umbilical vein. The technique employed has been to make a transverse incision through the skin about 1 to 2 cm. above the umbilical cord. The skin is then reflected back on to the cord and an aneurysm needle passed behind the cord tissue. This is incised, the vein identified, and the catheter introduced.

Once the catheter is in position the transfusion is conducted as in any other case and technical difficulties are no more frequent.

Maintaining a Satisfactory Flow

Sometimes, even when one is confident that the catheter has been introduced correctly, blood fails to flow or flows only when the catheter is withdrawn a little. This suggests that a clot is present in the vein, and if it cannot be withdrawn through the catheter then the catheter should be carefully withdrawn while gentle suction is applied. It is usually

possible by this means to withdraw the clot, after which a straightforward exchange can be performed. Occasionally parts of the clot may be left behind and cause trouble for the first 30 to 40 ml. Clotting very rarely occurs in the apparatus, but when it does we have found it satisfactory to wash out the taps and cannula with sterile water, followed by saline, then to proceed as usual. Defects in the apparatus and sticking syringes should be rarities, avoided by scrupulous care in their maintenance and preparation. No technical difficulties were encountered in 217 of our 250 "adequate" exchange transfusions. In the remainder the difficulties were as follows: introducing the catheter, 10 cases; clotting in apparatus, 5; leaking apparatus, 4; sticking syringes, 4; maintaining the flow, 10.

General Management

Oxygen Therapy.—Oxygen is not required in the uncomplicated case, but should be available for any baby who becomes cyanosed or distressed. A plastic funnel covering the baby's face is usually satisfactory, but in very ill infants a more efficient method is required. On three occasions the whole procedure has been carried out in an "isolette" incubator, because the infants were premature, grossly anaemic at birth, and showed signs of heart failure. Recently we have used a "perspex" box which fits over the baby and cradles frame as far down as the groins (Fig. 4).

FIG. 4.—Apparatus for oxygen therapy.

By placing two hot-water bottles in the box a temperature of 85° F. (29.4° C.) can be maintained. A concentration of 50 to 60% oxygen is achieved with a flow rate of four litres a minute, and under these conditions the carbon dioxide concentration remains less than 1%. A swinging panel is provided in one wall of the box so that any necessary attention can be given to the baby. Severely affected babies benefit from a period in oxygen both before and after the transfusion.

Use of Calcium.—Theoretically, hypocalcaemia and tetany may be induced when large amounts of blood collected into citrate are used for transfusions of this kind. Therefore many workers (Wallerstein, 1948; Wiener and Wexler, 1949; Diamond *et al.*, 1951, 1952) recommend that calcium gluconate should be given at the end of, or periodically during, every exchange transfusion. We have not investigated this problem biochemically, but clinically have not recognized any signs of tetany. We gave calcium gluconate to four babies whose condition seemed unsatisfactory without any obvious explanation, but were not convinced that it produced improvement in any case. It is possible that, in removing 200 ml. of plasma from the donor blood, we also remove the main excess of citrate, but we have on occasion used whole blood without apparent ill effect.

Use of Heparin.—We have never thought it desirable or found it necessary to use heparin as advocated by Vogel (quoted by Wallerstein, 1947) and Wiener (1946, 1947, 1949).

After-Care

In the straightforward case, the baby's management following exchange transfusion does not differ from that of the normal newborn.

Antibiotics and Chemotherapy.—The prophylactic use of penicillin and sulphadiazine in all cases was recommended by Diamond *et al.* (1951, 1952). At one time 48 hours' penicillin therapy formed part of our routine in a proportion of cases, but as we found that a high percentage of organisms in the hospital concerned were resistant to penicillin we have abandoned this practice. Infection due to exchange transfusion has never occurred in our cases so far as we know. In the occasional case in which infection appears to be a real risk due to an undue amount of manipulation we have preferred to use streptomycin or chloramphenicol prophylactically.

Vitamin K.—This is given intramuscularly at birth as a routine in all cases, and has been continued for five days in many. We feel that this continued administration is not essential. Diamond *et al.* (1952) no longer recommend the use of vitamin K.

Haematinics.—There is no rationale for giving haematinics in this disease.

Breast-Feeding.—We encourage breast-feeding unless there is some other contraindication. Among over 1,000 cases of haemolytic disease we have recognized only two cases of prolonged haemolysis due to transmission of antibody in the mother's milk.

Complications of Exchange Transfusion

Many hazards have been attributed to exchange transfusion, and some apply no matter what route is used, while others concern the use of only one particular method.

Sepsis.—This should be an extremely rare sequel, and we have indicated the steps we take to prevent it in cases exposed to more than average risk. Van Loghem and Bartels (1949) recorded four deaths from infection in their series.

Air Embolism.—Wiener and Wexler (1949) have criticized the umbilical vein route on the grounds that there is a great risk of air embolism. Pickles (1949) and Mollison (1951) also list this as a possible complication. We have never experienced this calamity and consider that the use of a transparent catheter should ensure that no air enters through its lumen. Air could enter the baby by passing up the umbilical vein alongside the catheter, but this can be prevented by tying a ligature round the cord and catheter, or by closing the vein tightly round the catheter by means of an artery forceps. Van Loghem and Bartels (1949) recorded deaths from air embolism, but they elected to use rubber rather than plastic catheters.

Thrombosis of Portal Vein.—Wiener and Wexler (1949) give this as a complication, but it has never happened in our experience.

Perforation of the Umbilical Vein.—This risk, which diminishes with the experience of the operator, is always present. Unless perforation occurs within the abdomen, no serious harm is likely to result. We have made a careful examination of the umbilical vein in all of our fatal cases, but, apart from minimal bruising, have discerned no injury.

Reaction Due to Incompatible Transfusion

Van Loghem and Bartels (1949) reported this as a cause of death in their series, and obviously the risk exists as with any transfusion. We feel that in the newborn, and particularly using exchange transfusion, the dangers are less likely to be serious than in simple transfusion of older subjects. On two occasions we unwittingly used blood which was frankly incompatible.

Case 1.—A baby was given Rh-positive instead of Rh-negative blood by mistake. He pursued an uneventful course; in particular, only mild jaundice, lasting less than one week, developed, and further transfusion was not required. We were able to

demonstrate that the transfused cells were eliminated rapidly although no free antibody was detected in the infant's cord blood.

Case 2.—This was an infant with an Rh-negative mother and an Rh-positive father, but antibodies had not been demonstrated antenatally. The routine cord-blood specimen was Coombs-positive and early jaundice occurred. Exchange transfusion was carried out, using Rh-negative blood of the same ABO group as the baby, but without full compatibility tests. It was later discovered that haemolytic disease was due to ABO incompatibility. This infant also progressed satisfactorily, and, although all transfused cells were eliminated within fourteen days, no additional transfusion was required.

Overloading of the Circulation

This is a very real danger in infants grossly anaemic at birth and one that we encountered early in our experience. A baby admitted from the domiciliary practice of the hospital had a capillary haemoglobin level of 7.3 g.% at seven hours. As his condition remained satisfactory during exchange transfusion, we decided to give an additional 70 ml. of blood slowly at the end of the exchange. The baby became deeply cyanosed and stopped breathing. The catheter was disconnected and blood poured from it, obviously under increased pressure. We allowed bleeding to continue until the pressure was normal. The baby rallied, only to die three hours later, and at necropsy signs of heart failure were found. Because of this early experience we give additional blood only to infants fit at the start and throughout the transfusion, and then never more than 30 to 40 ml. If there is the slightest doubt we do not expose the infant to this risk.

That the possibility of heart failure can never be ignored was once again made clear to us only recently. A baby was born outside and admitted with severe clinical disease. The venous pressure at the start of the transfusion was normal, but, even so, we discarded 10 ml. before carrying out the exchange. At 510 ml. out/500 ml. in, the baby was well and the venous pressure normal. We decided to replace the 10 ml. to complete the transfusion. Having done so, we disconnected the catheter, and simultaneously observed the infant to be deeply cyanosed and the venous pressure to be very high. The removal of 40 ml. of blood, artificial respiration, and the intravenous and intracardiac administration of stimulants were of no avail. The infant died, and at necropsy evidence of heart failure was found. From this we learnt two important lessons: first, 10 ml. of blood is enough to precipitate fatal heart failure, and, second, one should always carefully assess the severity of the case before undertaking treatment. The haemoglobin level at the start of exchange transfusion was only 6 g.%, but unfortunately we did not make this estimation until after the baby was dead.

Before beginning treatment we would recommend that the venous pressure be measured, and, if desired, the manometer described by Mollison (1951) may be used for this purpose. If the pressure is higher than 10 cm. more blood should be withdrawn than is given until the pressure is normal. Most infants with a cord haemoglobin level of 11 g.% (75%) or less appear to benefit by having less blood injected than is withdrawn. As a very rough guide, the negative balance should be about 10 ml. for every 10% of haemoglobin below this level. Whenever the cord haemoglobin is less than 7.4 g.% (50%) we feel that the transfusion should be carried out at a negative balance, even if the venous pressure is within normal limits.

If the venous pressure is high we aim to reduce it as early as possible by removing from the baby 20 ml. of blood and replacing it with 10 ml. This is repeated until the venous pressure is reduced to normal. We regard the high venous pressure as partly compensatory for the anaemia, and consider that the above routine, using blood with a haemoglobin content of about 17 g.%, has the advantage of raising the haemoglobin level at the same time as the venous pressure is reduced. Diamond *et al.* (1952) also use this system, which we suggest is better than the practice of removing 50 ml. of blood from similar cases before injecting any.

Reaction of the Infant to Exchange Transfusion

In about 40% of infants treated by exchange transfusion the general condition deteriorates during transfusion, and in many cases no obvious cause is evident. The risk does not appear to be related in any simple way to the baby's condition at the start, to the birth weight, to the technical difficulties encountered, or to the rate of exchange. Certainly, severely ill babies usually give cause for anxiety throughout the transfusion, but it is not uncommon for an infant with relatively mild disease and in good condition at the start to deteriorate during the transfusion. Collapse is usually due to one of two factors.

(1) **Heart Failure.**—This is usually, but not always, limited to babies grossly anaemic at the start, with a high venous pressure. The main features observed in these cases are cyanosis (readily observed in the lips, but often first noticed because the blood being withdrawn from the baby has become dark in colour), rapid shallow respiration, increased heart rate, and a high venous pressure. The baby, having been active and crying, may become limp and silent or have sighing or grunting respiration with some frothing at the mouth. Oxygen, withdrawal of blood until the venous pressure becomes normal, and slowing the rate of the procedure often result in improvement. If, in spite of this, the baby's condition deteriorates, we would suggest that the transfusion be stopped and the baby placed in an oxygen box. We have done this with benefit in eight instances, and have had no technical difficulty in restarting and completing the transfusion. The catheter is clamped and left *in situ*, and is replaced by a new one when the transfusion is recommenced; alternatively, the cord may be ligated.

(2) **Shock.**—Although some babies show some degree of shock, becoming pale and quiet, with rapid shallow respirations, this is seldom severe enough to cause great anxiety, and they usually recover with warmth and slowing of the transfusion. However, in one or two such infants we have experienced difficulty in withdrawing blood. The giving of 20 to 30 ml. of blood without any being withdrawn resulted in dramatic improvement: the procedure once again became easy and all remained well. But if there is the slightest possibility that the clinical deterioration may be due to heart failure, extra blood should not be given. It is wiser to stop the transfusion, because placing the baby in an oxygen box brings improvement, whichever the cause, and the clinical distinction may be very difficult.

We foresee that full investigation of the biochemical and other factors involved may eventually explain the deterioration in the clinical condition of some of these cases.

Conclusion

We believe that exchange transfusion forms an essential part of the treatment of babies suffering from relatively severe haemolytic disease of the newborn. In practical hands it is a safe and satisfactory procedure. Linked with laboratory prediction beforehand and skilled care afterwards, it should ensure a satisfactory outcome in the great majority of cases.

The cases with which this report is concerned have been collected from a large part of Northumberland and Durham, and but for the good will of the obstetricians, family doctors, and antenatal clinic staffs this material could not have been concentrated in one centre. The Regional Blood Transfusion Centre in Newcastle-upon-Tyne has undertaken the antenatal and cord-blood serological tests necessary for the diagnosis. It is because of the efficiency of this service that such a large proportion of cases have been diagnosed antenatally, and this has materially contributed to the results. As this report deals with cases collected over a period of eight years in the Newcastle-upon-Tyne group of hospitals, it is obviously impossible to mention by name all those to whom we are indebted for help. We would like to thank our medical and nursing colleagues in these hospitals for their continuous help.

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A STUDY OF THE ACTION OF TRICYCLAMOL CHLORIDE

BY

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In the search for efficient treatment of gastric and duodenal ulcer the primary object of prolonged reduction of free HCl concentration in the gastric juice has been achieved (Douthwaite and Thorne, 1954). It was postulated that the failure of single large doses of antacids was due to their rapid expulsion from the stomach, especially in cases of duodenal ulceration. Drugs which will reduce the rate of emptying should therefore prolong the antacid effect; at present this is obtainable only by the slow sucking of alkaline or buffering tablets. The difficulty of controlling nocturnal secretion might in this way be overcome.

The belladonna alkaloids and, to a far greater extent, hexamethonium (Douthwaite and Thorne, 1951) by injection, have been used for this purpose.

The object of this communication is to report our experiences with tricyclamol chloride (DL-N-methyl-3-cyclohexyl-3-hydroxy-3-phenylpropyl pyrrolidinium chloride), shown in animal experiments to have an antispasmodic and parasympatholytic action. It is an odourless crystalline substance, which is freely soluble in water. It may be given by mouth or by subcutaneous injection. The doses employed have varied from 25 to 100 mg. and are indicated in respect of each experiment.

Our object has been to test the effect on gastric and duodenal motility and tone; the influence on gastric acidity; and the effect of a single dose of antacid on the pH of the gastric juice during the action of tricyclamol.

Tricyclamol chloride

Methods

The effects of tricyclamol upon gastric and duodenal motility were observed on the x-ray screen during a barium meal and films were taken. Comparison was made with barium meals given without the drug. The influence of tricyclamol on gall-bladder emptying was shown by cholecystography with and without a dose of tricyclamol.

The effect of tricyclamol on the pH and levels of free and total acid of test-meal samples were observed and compared with control meal samples obtained without the drug. In three patients tricyclamol was given immediately after passing a Ryle tube—50 mg. intramuscularly in two cases and 50 mg. orally in one case. The meal was eaten and samples of gastric contents were taken every 15 minutes. In a fourth patient 100 mg. of tricyclamol was given orally half an hour before starting the meal.

Two of the patients also received an alkaline mixture (aluminium hydroxide gel B.P.C., 8 ml.) immediately after swallowing the meal. The stomach was not emptied of its resting contents. We wished to discover how effective tricyclamol might be in reducing the acidity of gastric contents under ordinary conditions, since, in actual treatment of peptic ulcer, drugs given to decrease acidity are used in the presence of some secretions still in the stomach. To be of value the drug should reduce acidity in the presence of previously secreted gastric juice.

Three of the four patients were given a "standard breakfast" of one boiled egg, two slices of toast, and two cupfuls of tea. Such a meal allows the response of the stomach to normal food to be measured in terms of pH and acidity, and probably represents a more usual gastric stimulus than a gruel meal. It has the disadvantage of not being directly comparable to series of test meals done in the past, when gruel was commonly used for the meal. One of these four patients received a gruel meal.

In an attempt to reduce sampling error (James and Pickering, 1949), about 30 ml. of gastric contents was aspirated at each time. After agitation of the syringe contents, about 7 ml. of the mixture was retained and the remainder returned to the stomach: 5 ml. of each sample was titrated within 24 hours of collection. (Storage at 4° C. before the estimations.) The pH was measured electrometrically. Titration to pH 3 with 0.5N NaOH solution was taken to represent the level of free acid in the samples. The level of total acid was measured by titration to pH 7.

Results

1. *Effect on Gastric and Duodenal Motility and Tone.*—Radiological observation of barium meals showed that gastric, duodenal, and small-intestinal motility and tone were considerably reduced after a dose of tricyclamol. (Figs. 1 and 2 show typical appearances.) Yet in a patient with a partial gastrectomy and symptoms of the "dumping syndrome" emptying of the stomach occurred even more rapidly than usual when 50 mg. of tricyclamol was given intramuscularly before a barium meal. This was associated with extreme flaccidity of the stomach, very well seen on