REPLACEMENT TRANSFUSION AS A MEANS OF PREVENTING KERNIKTERUS OF PREMATURITY

BY

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The possibility of premature babies developing kernikterus from jaundice not due to haemolytic disease is now generally recognized (Aidin, Corner and Tovey, 1950; Zuelzer and Mudgett, 1950; Hsia, Allen, Diamond and Gellis, 1953; Billing, Cole and Lathe, 1954; Crosse, Meyer and Gerrard, 1955; Meyer, 1956).

In haemolytic disease kernikterus has been practically eliminated by the use of repeat replacement transfusion to wash out the excess of bilirubin, and this form of treatment therefore seems to be indicated for the prevention of kernikterus due to prematurity.

Since the beginning of July, 1955, bilirubin levels have been estimated each morning (and when necessary in the evening also) in all premature babies showing definite clinical jaundice during the first eight days of life; and replacement transfusion has been performed in each case in which the level reached 18-20 mg.% during this period or was rising so rapidly that it would probably have reached this level before the next morning. Haemolytic disease has been proved or disproved in each case by full examination of the blood of both mother and baby. The transfused babies have been followed up carefully to assess any damage (however small) which might have resulted from the jaundice or from the transfusion.

Material

The 1,320 babies studied were the total number of admissions to the three premature baby units under our care during the two-year period from July 1, 1955, to June 30, 1957.

The degree of jaundice was roughly estimated by blanching the skin, either by stretching or by pressure. If examined by daylight it soon became possible to decide whether the level of bilirubin had reached approximately 10 mg.% or not. If it appeared to have reached this level, blood was taken for bilirubin estimation and to exclude haemolytic disease. In two of the units blood was taken by femoral puncture, and in one by multiple heel prick.

Results

Number of Babies who Required Transfusion. Table 1 shows all premature babies admitted to the three premature baby units during the two years under investigation, and the number who required replacement transfusion for hyperbilirubinaemia not due to haemolytic disease. The 1,320 babies are divided into three birthweight groups: group A includes all babies up to 1,500 g. at birth, group B babies from 1,500-2,000 g., and group C babies from 2,000-2,500 g.

With the exception of group A, the percentage of babies requiring transfusion diminished as the birthweight increased. Because many babies weighing less than 1,500 g. die before they can develop hyperbilirubinaemia, the transfused babies are also given as a percentage of the babies at risk (babies alive at 48 hours) but even when this is done group A still shows the smallest percentage of babies transfused. The reason for this is difficult to understand unless it was due to the small numbers involved. It is of interest that this discrepancy was not present among the babies treated in Sorrento premature baby unit which deals with the highest proportion of small babies. In Sorrento during the past two and a half years, eight out of 207 babies weighing less than 1,500 g. at birth (group A) were transfused (3·9%). If only the 99 babies at risk (alive at 48 hours) are considered, 8·1% were transfused. For comparison, 8·5% of the babies at risk were transfused in group B, and 7·5% in group C. If by chance, one more baby in group A had been transfused, this would have raised the percentage in this group to 9·1%.

Of the total 1,320 premature babies admitted, 92 (8·4%) required replacement transfusion for hyperbilirubinaemia not due to haemolytic disease. It is of interest to find that the five cases of kernikterus which occurred during this series were all in group B.

Number of Babies who Required more than One Transfusion. If, after the first transfusion, the level of bilirubin rose again to dangerous levels, the same

TABLE 1
BABIES REQUIRING REPLACEMENT TRANSFUSIONS

Birth Weight	Total Admissions	Babies at Risk (alive at 48 hr.)	Babies Transfused		
			No.	% of total	% of babies at risk
Group A (Up to 1,500 g.) ..	262	137	8	3·1	5·8
Group B (1,500–2,000 g.) ..	564	499	49	8·7	9·8
Group C (2,000–2,500 g.) ..	494	464	35	7·1	7·5
Total	1,320	1,100	92	7·0	8·4

criteria as before were used as indications for a repeat transfusion.

Table 2 shows the number of transfusions required by each affected baby in each of the three birthweight groups. The proportions of transfused babies requiring more than one transfusion show the same variations as in Table 1 but of course the numbers concerned are extremely small.

Of all transfused babies, 19·6% required more than one transfusion to keep the bilirubin below a dangerous level.

All five babies who later showed signs suggestive of kernikterus required more than one replacement (one baby required four, one required three and the remaining three babies two each).

Mortality Due to Transfusion. There were two deaths among the transfused babies but only one was due to transfusion. This baby weighed 3 lb. 4 oz. at birth. The transfusion was technically easy and 250 ml. were exchanged but unfortunately no deficit was left. The baby collapsed and died five minutes after the completion of the transfusion. An autopsy showed that death was due to heart failure. Since this occurrence a deficit of 20-40 ml. has always been left.

The second death occurred in a baby which weighed 4 lb. 11 oz. at birth. This baby's mother had severe pre-eclampsia. The condition of the baby was extremely poor at birth and continued so. Jaundice developed rapidly and on the third day a replacement transfusion became necessary. The baby improved slightly after the transfusion but 12 hours later collapsed suddenly and died. An autopsy showed that death was due to gross atelectasis and the transfusion was not believed to have contributed to the death.

Babies in whom a Satisfactory Replacement was not Obtained. A replacement was called unsatisfactory if less than 80 ml./lb. (176 ml./Kg.) were exchanged.

Among the 92 first transfusions there was a failure to obtain a satisfactory replacement in three cases: this was due to spasm of the umbilical vein in two cases and failure to cannulate the umbilical vein in one.

There were also three failures among the 18 repeat transfusions. In each case the umbilical vein had been ligated after the first transfusion, and re-cannulation of the umbilical vein was impossible. In two of the three cases, the saphenous route was not attempted; in the third it was attempted but failed.

One baby comes into both these groups because the first transfusion was incomplete and the repeat transfusion failed. Five babies are therefore concerned, and two of these five babies developed kernikterus.

All six unsatisfactory replacements occurred during the early part of the period under review, and with our present technique failure should be rare. When spasm of the umbilical vein occurs, the replacement is now abandoned for one or two hours, after which time the spasm has usually relaxed. If it has not done so after this time the saphenous route is used. Repeat transfusions are now made easier by

TABLE 2
NUMBER OF TRANSFUSIONS REQUIRED

Birth weight	Babies Transfused	Transfused Babies				%Requiring more than one Transfusion
		No. of transfusions				
		One	Two	Three	Four	
Group A (Up to 1,500 g.) ..	8	7	1	—	—	12·5
Group B (1,500–2,000 g.) ..	49	38	9	1	1	22·4
Group C (2,000–2,500 g.) ..	35	29	4	2	—	17·1
Total	92	74 (80·4%)	14 (15·2%)	3 (3·3%)	1 (1·1%)	19·6

leaving the catheter *in situ* for several days in case a further transfusion should become necessary.

Age at First Transfusion. Fig. 1 shows the age at first transfusion for each of the three birthweight groups separately, and also for all cases together.

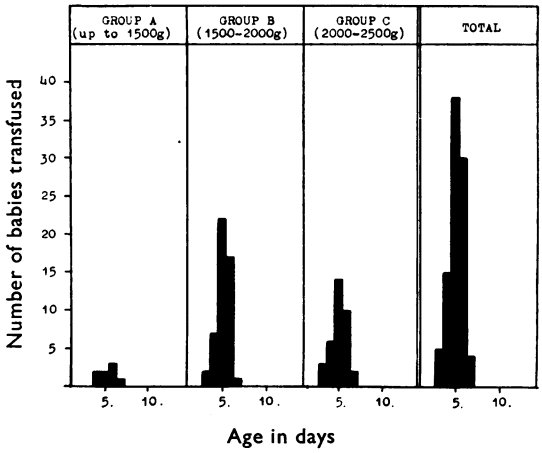

FIG. 1.—Age at first transfusion (92 babies).

In group A the first transfusion was performed between the ages of 3 days and 7 days, with the maximum incidence during the sixth day of life. In group B and C the first transfusion was performed between the ages of 2 days and 7 days and the maximum incidence was during the fifth day of life.

Of all 92 transfusions, five (5·4%) were undertaken on the third day of life, 15 (16·3%) on the fourth day, 38 (41·3%) on the fifth day, 30 (32·6%) on the sixth day, and four (4·4%) on the seventh day.

Of the five babies who developed kernikterus, the first transfusion was done on the third day in one case, on the fourth day in two cases, and on the fifth day in two cases.

Levels of bilirubin at which the decision was made to replace. (115 transfusions.) Fig. 2 shows these levels for each of the three birthweight groups separately, and for all cases together.

For 53 transfusions (46·1%) the decision was taken when the level of bilirubin was between 17 and 20 mg.%. In three of the four cases (3·5%) in which the decisions were made at lower levels, the jaundice was increasing so rapidly that it was not considered safe to leave the babies until the following morning; and in one case the reported level was believed to be incorrect because of the clinical severity of the jaundice.

For 58 transfusions (50·4%) the decision was made at levels over 20 mg.%. In the light of present knowledge this was too late because in all five babies who developed kernikterus, the decision to transfuse was made at levels over 20 mg.%. The decision to transfuse was made at levels over 20 mg.% for three out of nine transfusions (33·3%) in group A, for 32 out of 63 transfusions (50·1%) in group B, and for 23 out of 43 transfusions (53·5%) in group C.

When the decision to transfuse was taken at levels higher than 20 mg.%, this was usually due to lack of experience in judging the depth of jaundice. In some

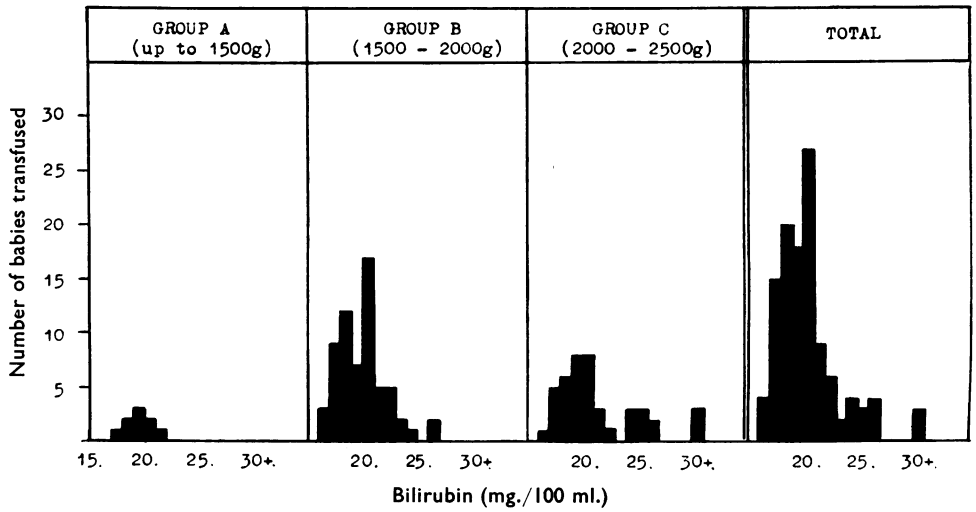

FIG. 2.—Level of serum bilirubin at which decision was taken to transfuse (115 transfusions).

cases the bilirubin level was first estimated when the critical level had already been reached; and in others the rate of increase in the depth of jaundice was not appreciated. It has been found that, with experience, the serum bilirubin level can be assessed clinically up to about 10-12 mg.%, but above that level it is impossible to judge the levels at all accurately clinically, and bilirubin estimations are now made much more frequently.

In the early months of the investigation different serum bilirubin results were frequently obtained by the various laboratories on the same blood. It was felt that the indications must be definite before embarking on what seemed a major operation, but as confidence in the safety of replacement transfusion was gained, and as the laboratory technique became more standardized, there was less hesitation in deciding to replace at lower and safer levels.

Highest Serum Bilirubin Levels Reached by Babies. Fig. 3 shows the highest bilirubin levels reached by babies in each of the three birthweight groups separately, and by all babies together.

In 29 (31·5%) of the 92 transfused babies the bilirubin level was kept below 20 mg.%; in 39 (42·4%) it rose to 20-22 mg.%, in 21 (22·8%) it rose to 22-27 mg.% and in three (3·3%) it rose above 30 mg.%. A rise to levels between 20 mg.% and 27 mg.% could be explained in each case by lack of experience either in judging the degree of the jaundice or in appreciating the rate of increase.

As regards the three babies in whom the bilirubin level rose to 30 mg.% or more, the following remarks may be of interest:

BABY R. (5 lb. 6 oz.) The bilirubin level reached 20 mg.% by the fourth day, but due to some misunderstanding the baby was not transfused. The level on the fifth day had risen to 30 mg.% and replacement transfusion was undertaken immediately. Luckily this child showed no signs of kernikterus and has developed normally.

BABY B. (4 lb. 1 oz.) This baby developed kernikterus and particulars are given in the section on the follow-up of all transfused babies.

BABY S. (5 lb.) This baby was slightly jaundiced on the first day and by the second day the bilirubin level had reached 14·6 mg.%. The level was not estimated that evening because the jaundice was not believed to have deepened. However the next morning the level was reported as 30 mg.% and an immediate replacement was performed. The child showed no signs of kernikterus and has developed normally.

These three babies were born during the first six months of the period under review. Bilirubin levels are now taken more frequently and such high levels are avoided.

The five babies who developed kernikterus were all in group B, and in each case the bilirubin level rose to 22 mg.% or more (two rose to 22 mg.%, two to 23 mg.% and one to more than 30 mg.%).

It is of interest that none of the 68 babies with levels below 22 mg.% developed kernikterus, while four of the 21 (19·2%) with levels of 22-27 mg.%, and one of the three (33·3%) with levels over 30 mg.% developed this complication.

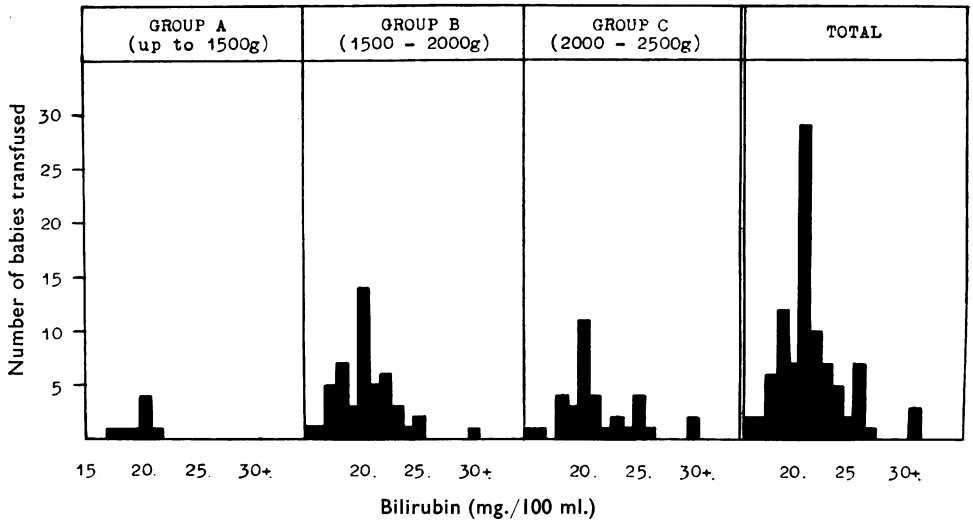

FIG. 3.—Highest serum bilirubin levels reached (92 babies).

No baby over 2,000 g. developed kernikterus. When babies under 2,000 g. are considered by themselves, four out of the 12 (33·3%) with bilirubin levels of 22-27 mg.% and the only one with a bilirubin level over 30 mg.% developed kernikterus. This was in spite of the fact that these high bilirubin levels were present for a relatively short time, except in the case of baby B.

Reduction in Bilirubin Level Achieved by Transfusion. It is impossible to give complete figures for this because technical difficulties often prevented the collection of all the required samples of blood. However, in cases in which the necessary samples were obtained, the reduction in the bilirubin level during transfusion usually varied from 45%-65%.

Follow-up of Transfused Babies. A great effort has been made to follow-up the 92 transfused babies. This has been difficult owing to the wide geographical area from which the units draw their cases. It was intended that each baby should be seen at three-monthly intervals until the age of at least 1 year. Actually 83 of the 90 surviving transfused babies have been followed to the age of 1 year, and one to the age of 9 months. The remaining six have moved to unknown addresses and all efforts to trace them have failed. There is, however, no reason to believe that any of these six babies are abnormal; when last seen by the doctor or health visitor they were considered normal.

The following five babies have developed signs which are probably due to kernikterus:

BABY G. (3 lb. 7 oz.) On the fourth day the bilirubin level rose from 16 mg.% in the morning to 20 mg.% in the evening; then unfortunately there was a delay of five hours before the baby was transfused. By this time the jaundice had increased (bilirubin 22 mg.%) and early signs of kernikterus had developed, i.e. head retraction, eye rolling and periods of apnoea during which cyanosis developed. This child is now spastic and possibly retarded, but is not deaf.

BABY K. (4 lb.) A transfusion was given on the fifth day when the bilirubin level was 21 mg.%, but a complete exchange was not achieved due to spasm of the umbilical vein after 100 ml. had been exchanged. The catheter was removed and the vein ligated. The following day the bilirubin level rose to 23 mg.%, but the umbilical vein could not be cannulated and the femoral route was not attempted. The bilirubin level began to fall the next day. No head retraction or other signs of kernikterus were seen and there were also no signs of birth injury or asphyxia during early life. The child is now mildly spastic, very emotional and probably slightly retarded, but is not deaf. In spite of the apparent absence of signs of kernikterus in the early days, this baby must be included because of the history of hyperbilirubinaemia.

BABY B. (4 lb. 1 oz.) This child was transfused on the third day (bilirubin 20 mg.%) and again on the sixth day (bilirubin 22 mg.%), but this time the umbilical vein went into spasm after 60 ml. had been exchanged. No further attempt was made because it was felt (wrongly) that the level of bilirubin would probably fall after this age. In fact the baby became more deeply jaundiced and signs of kernikterus developed on the ninth day when the bilirubin level was found to have reached 38 mg.%. This child is now definitely spastic and retarded, is having convulsions and probably has a hearing defect.

BABY C. (3 lb. 8 oz.) This child was transfused on the third day (bilirubin 18 mg.%). By the fourth day the bilirubin level had risen again to 20 mg.% but the baby was not transfused until six hours later when the bilirubin level had reached 22 mg.%. A third transfusion was carried out on the fifth day (bilirubin 20 mg.%). On the sixth day the bilirubin level had risen again to 18·4 mg.% but transfusion was not performed. By the seventh morning the baby had developed head retraction and the bilirubin level was again 22 mg.%. In spite of the head retraction a fourth transfusion was undertaken (with the hope of limiting the degree of brain damage) and after this the level of bilirubin fell steadily. This child now shows no spasticity but has been late in reaching all his mile-stones. There is a tendency to athetosis and there also appears to be some hearing defect.

BABY H. (3 lb. 15 oz.) This child was in a poor condition from birth. He had marked atelectasis and an enlarged liver, he also showed signs of cerebral irritation; he was not expected to survive. The first transfusion was undertaken on the fourth day (bilirubin 21 mg.%), a second on the fifth day (bilirubin 23 mg.%) and a third on the seventh day (bilirubin 20 mg.%). After this the level of bilirubin gradually fell. There were no definite signs of kernikterus at any time, but the general condition was very poor throughout the first week of life. This child is now spastic and probably retarded, but is not deaf. It is possible that this child's disability was the result of birth asphyxia, but he is included as a probable case of kernikterus because the bilirubin was allowed to rise to 23 mg.% on the fifth day.

From a study of these cases, it appears that all five were preventable, and much has been learnt from these failures.

A better realization of the rapidity of the rise in the level of the bilirubin by more frequent estimations during the critical period, thus enabling transfusions to be undertaken at lower levels, would have been helpful in all five cases.

The realization that the bilirubin could still rise to dangerous levels after the sixth day of life would have helped Baby B.

A reduction in the time between taking the actual blood sample and starting the transfusion might have saved babies S and C.

Better technique to avoid incomplete exchanges might have helped babies K and B, i.e. a period of rest to allow venous spasm to relax, leaving the

catheter *in situ* in case further transfusions become necessary, and the use of the saphenous route if the umbilical route fails.

Discussion

In order to assess the value of replacement transfusion in hyperbilirubinaemia not due to haemolytic disease, it is necessary to know what proportion of the premature babies admitted to our units would have developed kernikterus without such preventive treatment.

During the two years 1953 and 1954, the excessive use of vitamin K increased the number of cases of kernikterus occurring in our units (Crosse *et al.*, 1955), but before this unhappy episode, i.e. during the eight-year period 1945-1952, 1·08% of all admissions developed kernikterus, and approximately 70% of these babies died.

If this incidence (1·08%) is applied to the 1,320 admissions during the two years under review the expected number of cases of kernikterus would be 14. Of these, nine or 10 would have died, and four or five would have survived but suffered cerebral palsy. Instead, one baby has died (from transfusion) and five babies have developed cerebral palsy, two of whom are only slightly affected. If certain failures in diagnosis and technique had not occurred, these five cases might have been prevented. (Unfortunately the bilirubin level was allowed to rise above 22 mg.% in each case.)

Until some better method of preventing this important and dangerous complication of prematurity becomes available (e.g. conversion of the lethal indirect-acting into the harmless direct-acting bilirubin; or reduction of the rate of breakdown of the red blood cells so that the immature liver can cope with the reduced amount of bilirubin) replacement transfusion appears to be the only way of coping with the situation.

To avoid failures such as those described it is obviously necessary to keep the bilirubin level below 20-22 mg.% at all times, and this entails an exacting regime. In all hospitals where premature babies are treated, it is necessary to have a sufficient number of experienced nurses and doctors who can decide when the bilirubin level is approaching 10-12 mg.% and promptly take blood samples for laboratory estimation. Accurate estimations must be made on these samples, and the bilirubin level promptly reported. If the level is over 18 mg.% replacement should be performed with as little delay as possible. If the bilirubin level is rising rapidly a decision to replace may be made at a lower level, especially if the decision has to be made in the evening, with a long night ahead and the difficulty of assessing the degree of jaundice in artificial light and the reduction of laboratory facilities. In order to have some idea of the rate of rise in the level of bilirubin, the first estimation should not be left too late.

Full cooperation with the blood transfusion service is necessary to avoid undue delay between deciding to transfuse and performing the transfusion.

Medical staff with experience in replacement transfusion must be available at all hours of the day and night, and two assistants (nurses or medical students) should also be available.

Summary

The development of jaundice has been carefully observed in 1,320 premature babies admitted to three premature baby units during a period of two years, and exchange transfusions have been undertaken in 92 babies (8·4%) who developed hyperbilirubinaemia not due to haemolytic disease.

Of the transfused babies, 19·6% required more than one transfusion.

There were two deaths among the 92 babies transfused (115 transfusions), but one of these deaths could not be attributed either to the transfusion or to kernikterus.

The highest bilirubin level reached was less than 20 mg.% in 31·5%, 20-22 mg.% in 42·4%, 22-27 mg.% in 22·8%, and over 30 mg.% in 3·3%. No baby with a bilirubin level below 22 mg.% developed kernikterus, but 19·1% of those with levels of 22-27 mg.%, and 33·3% of those with levels over 30 mg.% developed this complication.

Of the 92 transfused babies five later showed signs which were probably due to kernikterus.

Until some better way has been found to prevent or treat hyperbilirubinaemia not due to haemolytic disease, it seems that replacement transfusion is the best way of preventing kernikterus.

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