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THE MANAGEMENT OF HAEMOLYTIC DISEASE OF THE NEWBORN

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Haemolytic disease of the newborn can be predicted with certainty before delivery. The diagnosis can be established within minutes of birth, and with the use of exchange transfusion the mortality need only be of the order of 2% of live-born infants with this disease. Yet in England and Wales during 1952 the recorded mortality was 14%. This represents a loss of 435 lives in the year, but we believe that 367 of these infants might have been saved. This needless loss of a life each day constitutes a challenge we must not ignore.

Experience in the Northern Region, 1952-3

The purpose of this article is to describe our recent experience of this disease in the Northern Region, to serve as a basis for comparison. We deal mainly with 1952 and 1953 because it was only in late 1951 that spontaneous delivery and exchange transfusion was proved to be the treatment of choice for infants with this disease.

The management of haemolytic disease of the newborn in this region is based on the following facts, some of which are generally accepted, while others have emerged from our experience during the past six years: (1) At least 5 out of every 1,000 babies in the North of England will suffer from haemolytic disease of the newborn. (2) Of 100 such babies 10-15 will be stillborn. (3) Of 100 live-born babies with this disease, 60 will require transfusion sooner or later, while the remaining 40, being affected to a lesser degree, will survive without treatment. (4) For those requiring treatment, early exchange transfusion is superior to simple transfusion (Mollison and Walker, 1952). (5) Premature induction has no routine place in the management of this condition (Mollison and Walker, 1952).

Although blood-grouping tests will enable practically 100% of cases to be predicted antenatally, there are no reliable means of forecasting severity; therefore hospital delivery has been offered to all immunized Rh-negative mothers. Three outlying hospitals have provided for their immediate areas, while the Newcastle group of hospitals has provided for the remainder.

Points Considered

We have tried to judge the adequacy of the arrangements by considering the following points: (1) The number of cases of the disease predicted in relation to the number expected, which affords a measure of the completeness of antenatal supervision. (2) The selection of cases for treatment, on which will depend the ultimate prognosis for the affected infant. (3) The survival rate in affected babies, by which we may judge the efficiency of treatment.

Incidence

The variations in the incidence of haemolytic disease of the newborn in 1952 and 1953 are shown in Table I. In each year 25 of the expected 27 stillbirths were recognized. Table II shows that, as serological facilities become more generally used, so the incidence of haemolytic disease of the newborn apparently rises.

TABLE I.—Variations in Incidence of Haemolytic Disease of the Newborn, 1952-3

Area	Year	Total Births	Expected No. H.D.N.*	H.D.N. Diagnosed	Cases not Predicted		Incidence per 1000 Total Births
					No	%	
Northumberland	1952	13,399	67	73	—	—	5.4
	1953	15,022	75	61	14	19	4.0
Durham ..	1952	26,532	133	99	34	25	3.7
	1953	25,748	132	139	—	—	5.2
Cumberland†	1952	4,977	25	13	12	48	2.6
	1953	4,960	25	18	7	28	3.6
North Riding ..	1952	9,292	46	17	29	63	1.8
	1953	8,849	44	31	13	30	3.5

*Expected number of cases of haemolytic disease of the newborn calculated on an incidence of 5 out of every 1,000 total births.

†Although part of Westmorland comes within the Northern Region, there is a tendency for cases to drain to hospitals outside this region; we have felt that any figures for this county could not be representative, and have therefore excluded them.

TABLE II.—Variations in Incidence of Haemolytic Disease of the Newborn Per 1,000 Total Births, 1948-53

Area	1948	1949	1950	1952	1953
Northumberland ..	3.5	4.7	5.8	5.4	4.0
Durham ..	1.6	2.5	3.5	3.7	5.2
North Riding ..	0.4	1.7	1.5	1.8	3.5
Cumberland ..	0.75	2.1	1.7	2.6	3.6

In 1952 75 cases were missed, while 34 were missed in 1953. We assume that, although some of these infants would be stillborn and others so mildly affected as to require no treatment, lives have been lost unnecessarily.

Unfortunately, only 75% of cases in 1953 were predicted antenatally, the remaining 25% being diagnosed only after delivery. Of the 49 Northumberland and Durham cases not predicted, 42 were because of failure to test for antibodies between the 32nd and the 36th week of pregnancy. Technical error and the presence of rare antibodies accounted for only four and three cases respectively. Unaccountably, a number of mothers had been tested in one or more previous pregnancies, yet not in the current one.

Northumberland and Durham

Northumberland and Durham (including Newcastle and Tyneside, but excluding Sunderland and Stockton) are regarded as one area because in the two years under review all women resident here and found by routine antenatal tests to be "Rh-negative with antibodies" were offered delivery in one of the Newcastle group of hospitals. In each year four mothers, although living in the North Riding of Yorkshire, were delivered in a Newcastle hospital, and these cases are considered here.

Method of Treatment.—Where treatment was indicated we have used exchange transfusion, performed within nine hours of birth. By the umbilical vein route we have aimed to exchange 80 ml. per lb. (176 ml. per kg.) body weight,

using blood concentrated so as to have a haemoglobin value of approximately 17 g.%. There were no technical failures in 1952 and 1953.

Selection of Cases for Treatment

We have found that the haemoglobin and bilirubin levels in cord blood provide reliable criteria of severity, enabling one to select, within an hour of birth, practically all infants requiring treatment. Obviously some babies are so seriously affected that to await the results of laboratory tests is not only unnecessary but may be dangerous.

Since late 1951 the following have been our indications for exchange transfusion, and we think they apply to both mature and premature infants: A Coombs-positive baby with a cord Hb level of 14.8 g.% or less, and a cord Hb level of 14.9 to 17.7 g.% associated with a bilirubin level greater than 2.7 mg. per 100 ml. No infant with a cord Hb of more than 17.7 g.% has received exchange transfusion.

In our early experience cord-blood samples were often unsatisfactory because of errors in collection. With practice, satisfactory specimens can be collected with certainty, as illustrated by the following facts. In one hospital, 152 ideal specimens were collected from 159 live-born affected infants—that is, 96% of cases. Contrast this with 70 babies born in other hospitals. Ideal specimens were collected in only 25 instances, while a further 22 specimens were suitable only for one or other estimation—that is, 35% were absolutely satisfactory.

In those cases in which the cord-blood samples were not ideal we have been guided by whichever result was available. In practice this has usually been the cord bilirubin level, and we have treated any infant with a value greater than 2.7 mg. per 100 ml.

It is the practice in this region to collect clotted cord blood from the babies of all Rh-negative mothers, even when antibodies have not been detected antenatally. Thus, in 1953, 21 of the 49 cases not predicted antenatally were discovered on the routine Coombs-testing of cord blood, and, moreover, in each case the specimen was suitable for bilirubin estimation.

If cord-blood values were not available we have relied on clinical criteria.

Results

The 1952 and 1953 figures for live births and stillbirths are given in Table III. In Table IV the 1952 and 1953 figures

TABLE III.—*Northumberland and Durham: Results in 1952 and 1953*

Place of Birth	1952		1953	
	Live Births	Stillborn	Live Births	Stillborn
Newcastle group of hospitals	109	11	108	16
Eleven other hospitals (not affording special facilities)	15	8	23	0
Born at home	15	2	37	0
Total	139	21	168	16
	160		184	

TABLE IV.—*Treatment and Survival in Relation to Place of Birth (Northumberland and Durham, 1952 and 1953)*

Place of Birth	Total Live Births	Total Deaths	Not Treated		Treated with			
			Survived	Died	Exchange Transfusion		Simple Transfusion	
					Survived	Died	Survived	Died
Newcastle hospitals	217	7	87	1†	118	6	5	0
Other hospitals*	38	6	14	5	4	1	14	0
Home	52	11	20	4‡	5	3	16	4

* Not affording special facilities. † This baby (Case 7), mildly affected, died from pneumonia. ‡ One infant, surviving but with undoubted kernicterus, is shown as having died.

for treatment and survival are combined because the results in each year were almost identical. All deaths are included, whether directly attributable to haemolytic disease of the newborn or not. The mortality in cases not receiving special care is between 16 and 20%, which corresponds closely with that in a comparable local series during 1947–9 (Walker, 1950), a time when exchange transfusion was being performed only in isolated cases.

Seven deaths occurred in 217 infants born in the special hospitals and 6 in 38 infants born in other hospitals. The difference is startling. It is even more impressive when one considers that only four of the seven deaths in the Newcastle hospitals, but 16 out of 17 deaths in the "outside" cases, were the direct result of haemolytic disease of the newborn.

The three deaths in the Newcastle hospitals not attributed to haemolytic disease were from pneumonia in a baby mildly affected (Case 7) and from cerebral birth injury in a 3-lb. (1.4-kg.) (Case 6) premature infant. (See Case Notes.) Cerebral birth injury also accounted for the one "outside" death not attributed to haemolytic disease. Two further infants (Cases 2 and 3) died after treatment in the Newcastle hospitals and were regarded as not viable because at post-mortem examination they were found to fall into the pathological classification of hydrops foetalis.

Therefore in each year, of more than 100 affected infants born in the Newcastle hospitals, only one viable baby died from haemolytic disease. There can be no doubt that the low mortality is mainly due to the preferential use of early exchange transfusion. It is of interest that of 13 infants born "outside" and treated in this way three died from haemolytic disease of the newborn. We consider that two of these infants would have survived had they been born in hospital.

We observe that only five hospital cases came to "primary simple transfusion." All just failed to meet our criteria for exchange transfusion and all survived. None needed treatment within the first three weeks of life.

Most reassuring is the fact that we were able to predict mild disease not requiring treatment in the expected 40% of live-born infants. None of these infants died from haemolytic disease, nor have any of them developed sequelae that could be attributed to it. Similarly, 38% of infants born in other hospitals or at home survived without treatment.

Severity of Disease

We must consider whether the low mortality of 1952–3 could be accounted for by the occurrence in these years of an abnormally large proportion of mildly affected infants. In attempting to assess this, two points of comparison have been taken: (1) the cord Hb, which Mollison and Cutbush (1949) showed to be the best single criterion of severity; and (2) the birth weight, because babies of 5½ lb. (2.5 kg.) or less are exposed to a greater risk of developing kernicterus than are mature infants.

TABLE V.—*Cord Haemoglobin Distribution*

	All Cases Jan, 1949–Dec., 1953	1952	1953
Less than 13.3 g. %	33.5 } 49%	30 } 48%	29 } 44%
13.4–14.8 g. %	15.5 }	18 }	15 }
14.9–17.7 g. %	43 }	46 }	48 }
More than 17.7 g. %	8 } 51%	6 } 52%	8 } 56%

For practical purposes the distribution of cord Hb values in the cases under consideration follows the same pattern as that for our total series (Table V). Therefore, in this respect, there has been no unconscious bias in favour of the 1952–3 results.

Again the findings shown in Table VI do not suggest that in these years we have seen a high proportion of infants exposed to little risk. However, we feel that they do give too optimistic a view of the chance of survival of premature

babies with this disease, for in our total experience the mortality rate in premature infants treated by exchange transfusion has been about 30%.

TABLE VI.—*Treatment and Survival in Premature Infants, 1952-3*

Live Births	Died	Not Treated		Exchange Transfusion		Simple Transfusion	
		Survived	Died	Survived	Died	Survived	Died
17	3	5	Nil	8	2*	1	1†

* One infant (Case 6) has already been referred to as having died from cerebral birth injury. The other (Case 5) died on the fourth day, and at necropsy death was attributed to pulmonary collapse. Neither pulmonary haemorrhage nor kernicterus was present in either case.
† Born at home.

Case Notes of Newcastle Hospital Deaths

1952.—*Case 1*: A third affected infant in the family. Cord Hb of 95% (14.4 g.). Died two hours after completion of exchange transfusion. No cause was found even at necropsy. *Case 2*: A premature baby born *in extremis* with a cord Hb of 30% (4.6 g.). Exchange transfusion was started within 30 minutes of birth, but he died during transfusion. The post-mortem findings suggested hydrops foetalis. *Case 3*: One of twins, the other being stillborn with frank hydrops. The previous pregnancy had resulted in hydrops foetalis. This infant had a cord Hb of 30% (4.6 g.). Exchange transfusion was started within 30 minutes of birth, but death occurred during transfusion. The post-mortem findings suggested hydrops foetalis.

1953.—*Case 4*: A third affected infant, born with a Hb of 38% (5.6 g.); treated by exchange transfusion, but died on the second day. At necropsy there was generalized bleeding and marked liver necrosis, but no kernicterus. The infant had received vitamin K, but we wonder whether the liver necrosis might have prevented its synthesis and that therefore the bleeding was the result of hypoprothrombinæmia. Unfortunately, we did not estimate the prothrombin in this case. *Case 5*: The third affected infant in the family. Birth weight 4 lb. 12 oz. (2,150 g.); treated by exchange transfusion. This infant developed mild jaundice, the bilirubin being 3.6 mg. per 100 ml. at the time of death. At necropsy death was attributed to pulmonary collapse and cerebral birth injury. *Case 6*: A 3-lb. (1.4-kg.) premature baby who died shortly after exchange transfusion, never having established normal respiration. At necropsy the clinical diagnosis of cerebral birth injury was confirmed. *Case 7*: A baby with mild haemolytic disease who died from pneumonia.

Sunderland

Only the cases delivered in hospital are considered here, as the "outside" cases from this area are included in the Northumberland and Durham group. There was a big increase in the number of cases treated by exchange transfusion in the second year (Table VII). No infant who left without exchange transfusion died, apart from the case of spina bifida. The percentage of infants requiring no treatment is surprisingly small.

TABLE VII.—*Treatment and Survival, Sunderland, 1952 and 1953*

Year	Total Live Births	Total Deaths	Not Treated		Treated with			
			Survived	Died	Exchange Transfusion		Simple Transfusion	
1952	12	1	4	0	2	0	5	1
1953	15	2	1	1	10	1	2	0
1952-3	27	3 (11%)	5	1	12	1	7	1

None of the infants weighed 5½ lb. (2.5 kg.) or less. The infant dying untreated in 1953 had mild haemolytic disease, but spina bifida was the cause of death.

North Riding of Yorkshire

Table VIII includes five 1953 cases delivered in this area, although resident in County Durham. It does not include,

for each year, four North Riding women who were delivered in Newcastle. Four North Riding women were delivered at home even though two of them were known to be immunized. All four infants survived, although three required simple transfusion.

TABLE VIII.—*Treatment and Survival in Hospital Cases: North Riding, 1952 and 1953*

Year	Total Live Births	Total Deaths	Not Treated		Treated with			
			Survived	Died	Exchange Transfusion		Simple Transfusion	
1952	6	2	0	1*	1	1	3	0
1953	24	3	7	0	1	3	6	0
1952-3	30	5 (16%)	7	1	2	4	9	0

* A premature baby with a cord Hb value of 17% died at one hour. It was not treated, being regarded as non-viable.

During 1953 there was a great increase in the number of cases predicted and therefore delivered in hospital, and a greater use of exchange transfusion. Similarly, the number of cases so mildly affected as to require no treatment has increased, and in 1953 comprised 29% of all cases. Almost equal use is being made of simple and exchange transfusion as a form of treatment, but no deaths occurred in the cases left without exchange transfusion.

Cumberland

In 1952 nine cases were predicted antenatally, and in eight of these the children were born in the special centre, while the other was delivered in another hospital. The latter was left untreated and developed kernicterus. Two cases were not predicted before birth: these infants were born at home and both died, one being too ill for treatment at the time of admission; the other received a simple transfusion, but died despite it.

In 1953 the disease was not predicted antenatally in four out of 14 live-born affected infants. One was delivered in the hospital, was diagnosed on cord-blood findings, and is included in Table IX. The other three were born at home; one died with kernicterus on the third day without having become anaemic; one was transfused during the first week and survived; the other, although severely anaemic at three months, survived without transfusion. There was only one premature infant in the two years; it was treated by exchange transfusion and survived.

TABLE IX.—*Treatment and Survival in Hospital Cases; Cumberland, 1952 and 1953*

Year	Total Live Births	Total Deaths	Not Treated		Treated with			
			Survived	Died	Exchange Transfusion		Simple Transfusion	
1952	8	1	2	0	2*	1	3	0
1953	11	2	5	1	3	1	1	0
1952-3	19	3 (15%)	7	1	5	2	4	0

* One of these infants unfortunately died at 25 days from pneumonia, but is counted as a survivor in this table.

Discussion

In the five years following the end of the war the national mortality rate attributable to haemolytic disease of the newborn remained remarkably constant at 0.75 per 1,000 related live births, despite laboratory facilities for the prediction of this disease. In 1952, however, there was a significant fall, and it is tempting to attribute this to the greater use that was being made of exchange transfusion.

Even so, in 1952 435 babies were certified as having died from this disease. As there were 690,000 births in that year, one can calculate that there would be 3,100 live-born cases of haemolytic disease of the newborn; therefore the mortality rate in these infants was 14%.

We claim that the mortality rate can be reduced to 2% of live-born infants in a centre offering specialized care. Therefore, in an average year, of 700,000 births, instead of there being 440 deaths, there should be only 63.

The provision of laboratory facilities for the prediction and diagnosis of this disease is justified only if the tests involved* can be translated into terms of lives saved. This saving of life is likely to be achieved only if all immunized Rh-negative women are delivered in hospitals affording special facilities. There is no way of predicting the severity of the disease before birth: in particular, in a first affected infant it may be very severe.

In 1953 two infants admitted from "outside" died during exchange transfusion, and already in 1954 one baby, born at home and severely affected, died in the ambulance while being brought to hospital. We believe that these infants would have survived had they been born in the special centre. Similarly, a number of babies were in poor condition on admission owing to the journey from home to hospital. Most people would agree that, rather than have such a journey, ill infants would benefit from a period of rest, warmth, and oxygen between birth and the time of transfusion.

Except in very exceptional circumstances, a "flying squad" available to go out and perform exchange transfusion is not the answer, for the transfusion forms only a part of the management of these infants. We contend that delivery in special hospitals should be readily available to all immunized Rh-negative mothers.

It is well to consider whether there is some minimal number of cases a year below which it is not worth while to try to provide special facilities. As a rough estimate we would say that a "centre" requires at least one exchange transfusion a month in order to keep in practice. Therefore no centre should deal with fewer than 24 cases a year—that is, a parish of 300,000 population, representing 5,000 births a year.

It requires experience to perform safe and adequate exchange transfusion, for in less-practised hands technical difficulties are common and often the intended amount of exchange is not achieved. Moreover, a smooth transfusion produces less injury to the infant, and, if one is preoccupied with keeping the transfusion going, observation of the infant tends to be less complete.

TABLE X.—*Effectiveness of Exchange Transfusion in Different Centres*

Place of Birth	Treated by Exchange Transfusion	Deaths in Viable Infants due to Haemolytic Disease	Further Simple Transfusion Required
Newcastle hospitals . . .	121	2	11
Other centres (combined)	33	7	13

Recommendations

1. Steps should be taken to try to achieve 100% prediction by antenatal blood-grouping tests.

2. Antibody-testing should be the responsibility of a limited number of laboratories, for only in this way can reliable results be obtained. Not only is considerable experience needed, but also a large panel of people with rare genotypes. This is necessary if the specificity of the antibody is to be determined—a piece of information that may be vital when it comes to selecting blood for the affected baby. The selection of blood is greatly simplified if full family serological details are available "on the spot" and if the mother's antenatal serum is available for compatibility tests. This implies that the centre undertaking antibody tests should be closely associated with the hospital of delivery.

3. As the severity of disease in the baby cannot be predicted with certainty before birth by antibody titrations or

by the previous obstetrical history, all cases should be delivered in a hospital affording the following facilities: the collection and delivery of satisfactory cord-blood specimens; a round-the-clock serological and pathological service; supplies of appropriate blood and means for full compatibility tests and concentrating cells; provision for the care and management of extreme ill, perhaps premature, babies; and means of performing adequate exchange transfusion.

4. A centre should serve an area in which there is a minimum of 5,000 births a year—that is, 25 cases of haemolytic disease of the newborn yearly.

5. In each area all arrangements concerning the care of these infants should be the responsibility of one person.

6. If for some special reason a "mother with antibodies" is delivered "outside" and the home doctor is confronted with a suspected case of haemolytic disease of the newborn, two specimens of cord blood—one heparinized or in Win-trobe mixture and one clotted—should be taken, and the special centre contacted immediately. It is pointless, if not dangerous, to rush the baby to hospital before this is done.

Everyone should be alive to the clinical evidence of disease, even in cases in which antenatal serological tests have either not been carried out, or, alternatively, appear to exclude the disease. In particular, jaundice in the first 24 hours of life is virtually diagnostic.

Summary

The management of 451 cases of haemolytic disease of the newborn in the Northern Region in 1952–3 is described.

Evidence is presented supporting the view that the incidence of this disease is 5 per 1,000 total births, and as serological antenatal tests become more fully used so this figure is more nearly approached.

Live-born affected babies have been studied in relation to antenatal prediction, place of birth, treatment, and result. The best results were obtained when cases were delivered in hospitals offering special facilities and treated by exchange transfusion where indicated (60% of live births). The mortality under this regime can be reduced to about 2%. If this level were attained throughout England and Wales 63 instead of the present 400 or more babies would die from this cause each year.

Various recommendations for the management of haemolytic disease are made.

We are indebted to our colleagues of the medical and nursing staffs of the Princess Mary Maternity Hospital, Newcastle General Hospital, Babies' Hospital, Newcastle-upon-Tyne, and the Queen Elizabeth Hospital, Gateshead, for the care of most of these infants. The obstetricians, staffs of antenatal clinics, and family doctors have generously allowed these "mothers with antibodies" to be delivered in a limited number of hospitals. Our thanks are extended also to Drs. J. S. Faulds, J. B. Heycock, and J. J. Tillie, who supplied us with case summaries of infants in their areas; the staffs of the Regional Blood Transfusion Service and area pathological laboratories, who performed the serological tests; Miss Kathleen Young, of the Regional Blood Transfusion Centre, who undertook much of the clerical work; and to Mr. G. Davidson, of the Child Health Department and Miss Joan Rockcliffe, of the Transfusion Service, who gave considerable technical assistance. Finally, it is a pleasure to acknowledge the help and guidance given us by the late Sir James Spence, professor of child health, and Mr. H. Harvey Evers, professor of obstetrics and gynaecology, University of Durham, and by Dr. W. G. Patterson, senior administrative medical officer, Newcastle-upon-Tyne Regional Hospital Board.

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*The minimum number of tests for any area can be conveniently arrived at by allowing for one test for each birth in the area.