REVIEW ARTICLE

HÆMOLYTIC DISEASE OF THE NEWBORN DUE TO Rh ISOIMMUNIZATION*

A TEN-YEAR REVIEW WITH EMPHASIS ON EXCHANGE TRANSFUSION

LOUIS LOWENSTEIN, M.D. and
MORRIS SABIN, M.D.,† *Montreal*

ERYTHROBLASTOSIS due to Rh incompatibility presents two basic problems in management, the antepartum inhibition of the hæmolytic process with maintenance of a viable fetus and treatment of the baby in the newborn period with prevention of kernicterus and death.

At present, there is no effective treatment of the isoimmunization process in the antenatal period. During the past decade, exchange transfusion has been established as a most important and useful form of neonatal treatment. It has decreased the incidence of kernicterus and has reduced neonatal mortality.[2, 3, 5, 6, 10-13]

The present survey was undertaken because it was thought that a detailed review of both clinical and laboratory features of exchange transfusion therapy over a ten-year period at the Royal Victoria Montreal Maternity Hospital would be of interest.

*From the Hæmatology Service of the Department of Medicine and the Department of Obstetrics and Gynæcology of the Royal Victoria Hospital and McGill University Medical School. This study was supported by the Federal-Provincial Grant No. 604-13-9.

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METHODS AND MATERIALS

The clinical observations and laboratory data were obtained from the records of the Royal Victoria Montreal Maternity Hospital. Hæmoglobin levels[7] and total serum bilirubin levels[8] were obtained from heel puncture blood. Serum antibody titrations in albumin were performed using Rh positive cells according to the method of Diamond and Denton.[4] The antibody levels listed in "Results" refer entirely to albumin antibody titres. Saline antibodies were not estimated serially because they are not as important in the assessment of the disease. A direct Coombs test was performed in all cases.

RESULTS

Major emphasis has been placed on the results of the five years from 1951 to 1955, since this period was associated with a more intensive investigation of cases of hæmolytic disease of the newborn, as well as with a greater degree of uniformity in management by a number of different pædiatricians. Hence, it will be presented first. The period 1946 to 1950 has been reviewed so as to emphasize certain aspects of these results.

TABLE I.

Year	*No. of E. fetalis / total deliveries*	*Incidence*	*No. treated with exchange transfusion*	*% exchange transfusion in all cases*	*% exchange transfusion in all live-born babies*	*No. live-born babies not given exchange transfusion*
1951	12 / (3132)	1 / 261	5	41.6%	45.4%	5
1952	21 / (3392)	1 / 161	9	43%	47.3%	5
1953	32 / (3317)	1 / 107	20	67.7%	70%	8
1954	18 / (3451)	1 / 191	12	66.7%	92.3%	1
1955	27 / (3329)	1 / 123	20	74.1%	87%	1
Total	110 / (16,621)		66			20
Average		1 / 151		60%	68.4%	

1. THE PERIOD 1951-1955

A. *Incidence.*

There were 110 cases of hæmolytic disease of the newborn due to Rh incompatibility during this period (Table I). Sixty-six (60%) received exchange transfusion.

The percentage of cases given exchange transfusions increased progressively, with the lowest value in 1951 (41.6%), and the highest value in 1955 (74.1%). The over-all incidence of hæmolytic disease of the newborn (Table I)

TABLE II.

Year	Total cases E. fetalis	Total perinatal mortality %	Total deaths			Deaths in 66 babies treated with exchange transfusion
			Ante-partum	Intra-partum	Post-partum	
1951	12	2 (16.7%)	1	0	1	1
1952	21	7 (33.3%)	2	0	5	3
1953	32	4 (12.5%)	1	2	1	0
1954	18	5 (27.7%)	4	1	0	0
1955	27	6 (22.2%)	4	0	2	1
Total	110	24	12	3	9	5 (7.5%)
Average		(21.8%)				

ranged from 1 in 107 to 1 in 261, and averaged 1 in 151 for the entire five-year period.

There were 24 cases of fetal and neonatal deaths and 20 live babies among the 44 infants who did not receive exchange transfusions (Table I). Eighteen of the 20 live-born infants were delivered between 1951 and 1953. In 1954 and 1955 almost all babies born alive received exchange transfusions. The percentage of exchange transfusions in all live-born affected babies increased from 45.4% in 1951 to 87% in 1955.

As shown in Table II, perinatal mortality ranged from a low of 12.5% (four cases) in 1953 to a high of 33.3% (seven cases) in 1952. The average perinatal mortality for the entire five-year period was 21.8% (24 cases). It is impossible to relate perinatal mortality to the frequency of administration of replacement transfusions (Tables I and II). When the perinatal mortality was divided into antepartum, intrapartum and postpartum periods, pertinent data were obtained. Twelve deaths occurred ante partum, three intra partum and nine post partum.

Five (7.5%) of the 66 babies treated by exchange transfusion died during the postpartum period. Four of the 20 live-born babies not treated with exchange transfusion died post partum. Seven of the nine postpartum deaths occurred from 1951 to 1953. Eight of the 12 antepartum deaths occurred in 1954 and 1955. Hence, during 1954 and 1955 the more dangerous period for the baby was before delivery, while from 1951 to 1953 the more dangerous period was after delivery. The number of cases involved do not permit a definite statement regarding the significance of this observation.

B. *Administration of Exchange Transfusions.*

1. Exchange transfusions were administered via the umbilical vein in 65 infants and in only one instance via the saphenous vein. The volume of blood administered ranged from 100 c.c. to 500 c.c. and averaged 357 c.c. This average value is equivalent to 50 c.c. of blood per lb. of body weight. In three cases of postpartum deaths the amounts of blood given were limited by the poor condition of the babies and ranged from 135 c.c. to 152 c.c.

TABLE III.

Year	No. of cases receiving exchange transfusions				Total No. exchange transfusions per year
	One transfusion	Two transfusions	Three transfusions	Four transfusions	
1951	5	0	0	0	5
1952	7	1	1	0	12
1953	20	0	0	0	20
1954	6	5	0	1	20
1955	12	6	0	2	32
Total	50	12	1	3	89

Single exchange transfusions were given to 50 babies (Table III). Multiple exchange transfusions were given to the remainder as follows: Twelve patients received two exchange transfusions, one patient received three, and three patients received four transfusions. Thus, there was a total of 89 exchange transfusions in 66 babies. The annual number increased progressively from five in 1951 to 32 in 1955.

TABLE IV.

No. of cases	Time of administration of first exchange transfusion	No. of neonatal deaths
	after birth	
44	3 hrs.	4
12	6 "	0
2	12 "	1
3	24 "	0
3	48 "	0
2	More than 48 "	0

2. *The time of administration* of each exchange transfusion was divided into six periods (Table IV). Forty-four exchange transfusions were given within three hours of birth, 12 within six hours, three within 12 hours, seven within 24 hours, nine within 48 hours and 14 were administered more than 48 hours after birth.

The first exchange transfusion was started within the first six hours of life in 84.8% of cases (Table IV). It is of interest that four of the five babies dying post partum were first transfused within three hours of birth.

TABLE V.

Number	Immune antibody titre	Neonatal death
1	0	0
4	1	0
5	2	0
5	4	0
10	8	0
12	16	1
19	32	3
7	64	1
1	128	0
1	1024	0

C. *Immune Antibody Titres.*

A wide range (0 to 1024) of immune albumin antibody titres was recorded ante partum (Table V). In 56 cases the titre listed is the highest recorded after a progressive rise. Only 10 cases did not have a rising titre. Forty-nine cases were in the 8 to 64 range of titre (Table V). Fourteen of the 16 babies who were given multiple exchange transfusions were also in this narrow antibody titre range. A titre of 32, present in 19 cases, was associated with the largest single group of multiple exchange transfusions (seven cases), and with three of the five postpartum deaths.

averaged 3195 g. Table VI shows that a greater proportion of premature infants than mature infants died in the neonatal period and required multiple exchange transfusions. Two premature deaths were in babies delivered by Cæsarean section because of probable hæmolytic disease of the newborn. The average length of hospitalization of the premature infants was 23.8 days as compared with 12.3 days for the mature infants. This difference may have been due solely to prematurity.

TABLE VII.

Gestation age (weeks)	No.	Neonatal deaths	No. given multiple exchange transfusion	No. of premature babies	Range of immune antibody titre
33	1	0	1	1	16
36	5	0	3	3	2-32
37	7	0	0	1	4-128
38	14	3	2	2	1-1024
39	7	1	1	0	1-32
40	24	1	7	2	0-64
41	6	0	0	0	8-32
42	2	0	2	0	16-64

Eight of the nine premature babies (Table VII) were born at 36 to 40 weeks of gestation and only one baby was born before the 36th week.

TABLE VI.

Baby	No.	No. given multiple exchange transfusions	No. given supplementary simple transfusions	No. neonatal deaths	Birth weight (grams) Range	Average
Mature	57	12	20	3	2530 - 4120	3195
Premature	9	4	2	2	1753 - 2500	2201

D. *Multiple Exchange Transfusions.*

As shown in Table VI, 12 mature and four premature babies were given multiple exchange transfusions.

E. *Supplementary Simple Blood Transfusions.*

A total of 22 babies were given supplementary simple transfusions of 30-80 c.c. of whole blood or packed cells (Table VI). Sixteen babies received one such transfusion, five babies received two transfusions and one baby received three transfusions. The numbers of supplementary simple transfusions given were not related to the time of administration of the initial exchange transfusion, the numbers of exchange transfusions given to each baby or to prematurity.

F. *Prematurity.*

Of the 36 babies receiving exchange transfusions nine were premature infants. Their birth weight ranged from 1753 to 2500 grams, and averaged 2201 g. The birth weight of the mature babies ranged from 2530 to 4120 g., and

There was no relationship between prematurity and the antepartum antibody titre (Table VII), which ranged from 0 to 1024.

G. *Effect of Exchange Transfusion on Hæmoglobin Level.*

The cord hæmoglobin value at birth was determined in 63 of the 66 babies treated with exchange transfusions. It was less than 15.6 g. % in 47 babies, ranging from 4 to 15.6 g. % and averaging 11.7 g. %. In 16 cases it was greater than 15.6 g. %, ranging from 16.2 to 22.8 g. % and averaging 17.9%. At discharge the heel hæmoglobin values ranged from 7.0 to 17.0 g. % and averaged 12.0 g. % (Table VIII).

TABLE VIII.

	Cord hæmoglobin at birth <15.6 g.%	Cord hæmoglobin at birth >15.6 g.%	Heel hæmoglobin at discharge
Number	47	16	57
Range	4-15.6 g.%	16.2-22.8 g.%	7.0-17.0 g.%
Average	11.7 g.%	17.9 g.%	12.0 g.%

The hæmoglobin level at the time of discharge was less than at birth in 43 babies and was more than at birth in 11 babies. In one case the same values were obtained and in two cases there was no initial hæmoglobin value available for comparison purposes. In general, then, there was a definite trend to increased anæmia at the time of discharge, regardless of the birth hæmoglobin levels.

This is further emphasized by the following observations in 10 of the 11 cases where the discharge hæmoglobin was greater than the initial values: Four of these cases had been given supplementary transfusions, three were given both supplementary and multiple exchange transfusions, and three were given only multiple exchange transfusions. Thus, it is possible that artificial elevation of the hæmoglobin may have taken place in these 10 cases.

H. *Serum Bilirubin.*

Total serum bilirubin values were recorded repeatedly in each of 41 cases. The maximal neonatal level ranged from 1.6 mg. % to 28.4 mg. %, with an average of 14.9 mg. %. This maximum value followed a progressive rise in the bilirubin level.

In 26 of these 41 cases, a variable degree of anæmia was present at birth. A comparison between the hæmoglobin at birth and subsequent levels of serum bilirubin is presented in Table IX. Anæmia was present at birth in all

TABLE IX.

Serum bilirubin Range (mg.%)	*No.*	*Hæmoglobin at birth 12.0-15.6 g.%*	*Less than 12 g.%*
10 - 15	9	7	2
15 - 20	12	10	2
>20	5	2	3

infants whose serum bilirubin reached 10 mg. %. The severest anæmias seemed to be in those infants whose bilirubin rose to over 20 mg. %, but the series is too small to definitely relate the severity of anæmia to the amount of hyperbilirubinæmia.

I. *Direct Coombs Test Following Exchange Transfusion.*

Every baby in this series had a positive direct Coombs test at birth, before treatment with exchange transfusion. The Coombs test was recorded in 24 cases after exchange transfusion, and in 12 cases it had become negative before the babies' discharge from hospital.

J. *Clinical Observations.*

Hepatomegaly, œdema and central nervous system changes were assessed and were correlated with anæmia and hyperbilirubinæmia.

TABLE X.

Hepatomegaly Degree in fingers' breadths	*No.*	*Associated œdema*	*Neonatal death*
0	28	0	0
1FB	6	1	0
2FB	17	2	2
3FB	6	2	0
4FB	1	0	0
5FB	7	4	3
6FB	1	0	0
Total.....	66	9	5

The degree of hepatomegaly ranged from no enlargement to 6 fingers' breadths below the right costal margin (Table X). In a total of 51 cases, the liver was within the normal range of 0 to 2 fingers' breadths. There was definite hepatomegaly in 15 cases. Three of the five postpartum deaths were in this latter group.

Œdema of mild degree was noted at birth in nine babies (Table X). Hepatomegaly was present in six of these babies.

There were detectable central nervous system changes at birth in six babies (Table XI). These changes consisted of respiratory depression, hypotonicity or hypertonicity. Four of these babies had associated hepatomegaly and five were known to be anæmic at birth. In the two cases in which serum bilirubin was obtained, a maximum level above 10 mg. % was recorded. There were only two babies with even a suggestion of kernicterus at the time of discharge.

The major clinical observations in the five infants who died post partum were as follows: One baby had only hepatomegaly. Four babies had both hepatomegaly and œdema. Three of the five babies had hepatomegaly, œdema and central nervous system changes. The hæmoglobin value at birth was known in four babies and ranged from 8.7 to 13.9 g. %.

TABLE XI.

Changes at birth in six babies	*Anæmia at birth*	*Hyperbilirubinæmia*	*Hepatomegaly*	*Possible kernicterus*	*Neonatal death*
			Fingers' breadths		
Decreased muscle tone.....	+	+	3	0	No
Respiratory and muscle tone depression.....	+	+	5	0	+
Hypertonicity.....	+	No	3	?	No
Respiratory depression.....	?	No	5	0	+
Respiratory depression.....	+	No	2	0	+
Respiratory depression.....	+	No	2	?	No

K. *Management of Labour.*

There were 57 vaginal deliveries and nine Cæsarean sections. Seven Cæsarean sections were performed because of previous erythroblastosis fetalis. Two of these seven babies were premature infants and died. Cephalo-pelvic disproportion was the indication for the remaining two Cæsarean sections. Medical induction was instituted successfully in three cases.

2. THE PERIOD 1946 TO 1950

In this five-year period the incidence of diagnosed cases of erythroblastosis fetalis was 1 in 262. There were 15 antepartum deaths (23.4%) and 21 neonatal deaths (32.8%), with a total perinatal mortality of 36 cases (56.2%) out of a total of 64 cases (Table XII).

TABLE XII.

	1946 - 1950		*1951 - 1955*	
	No.	*%*	*No.*	*%*
Antepartum and intrapartum deaths....	15	23.4	15	13.6
Postpartum deaths.....	21	32.8	9	8.2
Perinatal mortality.....	36	56.2	24	21.8
Live babies.....	28	43.8	66	78.2

The treatment of these infants during 1946 to 1950 is listed in Table XIII. Among the 49 babies who were born alive, 13 did not receive blood transfusions of any kind and nine died, and 23 babies were given simple blood transfusions and seven died. The remaining 13 babies were given exchange transfusions and five died. Exchange transfusions were not administered before 1948.

TABLE XIII.

Treatment of babies 1946 - 1950	*No.*	*Total postpartum deaths*	*Postpartum deaths in the 8 live-born premature infants*
No blood transfusion.....	13	9	2
Simple blood transfusion..	23	7	3
Exchange transfusion....	13	5	3

Twenty of the 64 babies during 1946 to 1950 were premature. Twelve of the premature babies died before birth and the remaining eight died in the neonatal period. Three of the latter infants were given exchange transfusions, three were given simple blood transfusions and two infants did not receive either form of transfusion (Table XIII).

3. BABIES NOT TREATED BY EXCHANGE TRANSFUSION—1951-1955

During this period 20 babies (18.2%) were not treated by exchange transfusion. Laboratory data were available in only 13 of the cases. In general, the disease in these infants was of a milder nature than in those treated by exchange transfusion. For example, the average hæmoglobin level at birth was higher by 2 g. %, and the hospitalization was 1.8 days shorter. At discharge the average hæmoglobin was 3.2 g. % higher. There were no cases with œdema or central nervous system changes during the neonatal period.

Ten of the 13 babies did not receive any special treatment. The remaining three were given simple blood transfusions, but in two of these cases there had been an unsuccessful attempt at exchange transfusion. The condition in these two cases was not as mild as in the others and successful exchange transfusion would have been a better treatment.

DISCUSSION

A. *Comparison of the 1946-1950 period with that of 1951-1955.*

It is apparent from the foregoing results that the treatment of hæmolytic disease of the newborn at the Royal Victoria Montreal Maternity Hospital has improved basically during the ten years from 1946 to 1955. The usefulness of exchange transfusion became apparent during the latter portion of 1946-1950 and it has become the mainstay of treatment in this disease.

A comparison of the results in the two five-year periods illustrates the value of exchange transfusion in reducing fetal wastage. The perinatal mortality was decreased from 56.2% during 1946-1950 to 21.8% during 1951-1955. This was due to a reduction in both antepartum and postpartum deaths (Table XII), with particular emphasis on the latter category. The improvement in the death rate is likewise reflected in the salvage of premature infants. Seven of nine premature infants survived during 1951 to 1955, whereas each of the live-born premature infants in 1946 to 1950 perished.

It is possible, however, that the aforementioned improvement may have also been due to a fundamental change in the hæmolytic disease with a diminution in its severity during the period extending from 1951 to 1955. This is suggested by the observation that the proportion of antepartum deaths was less during this five-year period (13.6% versus 23.4%), even though the antepartum management was subsequently the same as in the previous five-year period. Confirmation of this impression must await reporting of data from other centres.

The greater salvage of premature infants during the period 1951 to 1955 may be due, in part, to such a fundamental change. In the case of premature infants, part of this salvage must also be attributed to the improvement in nursing techniques which took place between 1951 and 1955. The major factor, however, was undoubtedly the institution of exchange transfusion therapy.

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B. *1951-1955.*

During this period, there was a progressive increase in the use of exchange transfusions as the treatment of choice for hæmolytic disease of the newborn. Increasing willingness to give multiple exchange transfusions to selected cases followed upon greater familiarity with the technique. This has been associated with a decreased incidence of neonatal death, notable in 1954-1955 (Table II).

The perinatal mortality (21.8%) for the entire five-year period includes a higher proportion of antepartum deaths during 1954 and 1955. These data emphasize the absence of control of the erythroblastotic process in the antepartum period, which remains the period of greatest danger to the baby. Our perinatal mortality statistics are similar to the 22.1% of Teate[11] and the 20% of Allen *et al.*[3]

Value of Timing of Exchange Transfusions:

In 56 cases (84.8%), the first exchange transfusion was administered within six hours of birth and five of these babies died. In the remaining 10 cases the disease was mild and the later administration of exchange transfusion did not have deleterious effects. Although early exchange transfusion is desirable, it is apparent that this procedure may not prevent death if the disease is sufficiently severe.

Additional Transfusion Therapy:

Multiple exchange transfusions and supplementary simple transfusions are comparable only because they are both given in the neonatal period. Multiple exchange transfusions have the primary purpose of treatment of a persisting hæmolytic process, as indicated by a recurrent rise in total serum bilirubin, often with an associated decline in the hæmoglobin level. In one-third of the series (22 cases), treatment with exchange transfusion, either single or multiple, required supplementation by simple transfusion of whole blood or packed cells to combat anæmia not associated with a rising serum bilirubin. It is possible that the numbers of single transfusions might have been reduced by employing packed red cells more liberally in the replacement transfusions.

It is noteworthy that multiple exchange transfusions did not cause any physical harm to the babies. Repeated use of the umbilical vein presented no difficulty.

Influence of Exchange Transfusion on Hæmoglobin Levels:

After replacement transfusions the neonatal hæmoglobin values tend to decrease. This is probably due to a number of factors, including some continuation of hæmolysis. Approximately one-quarter of the fluid administered in replacement transfusions was a citrate-dextrose diluent; this may have resulted in inadequate replacement and hence may have contributed to the anæmia. From the clinical point of view it is questionable whether this depressant effect on the hæmoglobin level is of importance, particularly if this level is not less than 12 g. %. However, only further studies, including follow-up during the first year of life, can result in a definitive opinion about this matter. In 10 cases where the hæmoglobin value was greater at the time of discharge than at birth there was a background of artificial supplementation by means of multiple exchange transfusions or simple blood transfusions.

Prematurity:

Neonatal deaths and administration of exchange transfusion were relatively more frequent in the nine premature infants than in the mature babies. A number of authors[1, 6, 9, 10] have commented upon the higher mortality rate of hæmolytic disease of the newborn in premature infants. It would seem then that premature infants are less able to withstand the effects of the hæmolytic disease than the mature ones.

This review indicates the inadequacy of gestation age as a criterion of prematurity. Eight of the nine premature infants were born between 36 and 40 weeks of gestation—that is, during the period when one would expect the baby to be mature.

Immune Antibody Titres:

The specific level of the immune antibody titre cannot be used as an accurate index of the severity of the hæmolytic disease. Thus, the most severely affected babies in this series were in a moderate range of titre (16 to 64) and there was no relationship between antibody titre and the need for multiple exchange transfusions.

A progressive antepartum rise in the titre is probably a much more important criterion for prognosis and management than is the specific value of the titre—especially when the latter is less than 128.[1, 11, 14] It must be realized when interpreting antepartum titres that they reflect a state of affairs in the mother, and give only a broad indication of events taking place in the baby.

Clinical Observations:

The various combinations of hepatomegaly, œdema, central nervous system changes and anæmia indicate that a severe degree of hæmolytic disease may be present without causing perinatal death. In some of these cases treatment with exchange transfusion was sufficient to keep the baby alive and to prevent further physical deterioration. In only two babies was there a suggestion of kernicterus at the time of discharge.

Five of the nine postpartum deaths were in the group showing the above clinical findings. Hence, there is a degree of severity of the hæmolytic disease which creates damage that cannot be reversed by one or more exchange transfusions.

Exchange transfusion is the only means currently available for removing serum bilirubin, immune antibodies and sensitized red cells from the blood (in 12 of 24 babies, the direct Coombs test became negative before discharge from hospital). It is a relatively simple and innocuous procedure and is usually well tolerated by the baby, provided that he is not already too severely stricken by the disease. Nevertheless, one must be cognizant of occasional complications such as thrombocytopenia, heart failure and ruptured spleen.

Termination of Pregnancy:

Only 13 babies were delivered before the 38th week of gestation. Seven pre-term Cæsarean sections in 66 cases does not constitute a major swing to early delivery in hæmolytic disease of the newborn, although it is about twice the over-all incidence for Cæsarean sections. There was no significant use of medical inductions for the early termination of pregnancy. In two cases early delivery by Cæsarean section did not ensure the babies' survival. Our own results and those of others[1, 3, 6, 10, 11] indicate that early delivery of erythroblastotic infants is not indicated routinely because of the dangers of prematurity.

Allen *et al.*[3] and Jacobs and Kohn[9] suggest that pre-term delivery is still the only way to prevent continued damage to the baby. This method of management may be considered in cases where there has been a history of previous death due to hæmolytic disease of the newborn, but even in these cases, because of the difficulty of correlating prematurity with gestation age, one should attempt to ascertain the maturity of the fetus—for example, by x-ray visualization of a femoral epiphyseal centre. A mature infant at 36 weeks of gestation has a better prognosis than a premature baby at 38 weeks.

C. *Babies not Treated by Exchange Transfusion in the 1951-1955 Period:*

The percentage of cases which did not receive such treatment (18.2%) compares with the incidence of 10-20% quoted by Diamond *et al.*[5] This group of cases is too small for a comparison with the much larger group who received exchange transfusions. One may infer that not all cases of hæmolytic disease of the newborn are of sufficient severity to warrant administration of exchange transfusion, but they constitute a definite minority and are not easily diagnosed. Treatment might be deferred if the serum bilirubin does not rise above 10 mg. % and if the hæmoglobin value is not less than 15 g. %.

The major objective in postpartum management is to prevent kernicterus or death of the baby, and because of the difficulty of early assessment of the severity of the disease it may be wiser to treat all babies with exchange transfusion, preferably within six hours of birth. This is emphasized by the fate of one of the two infants who received simple blood transfusion after an unsuccessful attempt at administration of an exchange transfusion. This baby died at 2 years, with cerebral palsy and kernicterus.

SUMMARY AND CONCLUSIONS

1. Findings are reviewed in 110 cases of hæmolytic disease of the newborn admitted to the Royal Victoria Hospital during 1951-1955 and 64 cases admitted during 1946-1950. During 1951-1955, 66 babies received a total of 89 exchange transfusions and this measure significantly improved the neonatal mortality. Consequently, early replacement transfusion has become the treatment of choice at the Royal Victoria Hospital.

2. The clinical and hæmatological features of the disease are reviewed. Anæmia, often present at birth, could not be correlated with the degree of subsequent hyperbilirubinæmia. Premature infants with the disease did not fare as well as mature infants. An increasing hyperbilirubinæmia was the most important single criterion for multiple exchange transfusions.

3. Exchange transfusion had certain limitations. A mortality of 7.5% in treated cases indicated that in severely affected babies the disease may be irreversible. Treatment with exchange transfusions was often followed by increased anæmia, and one-third of the babies so treated required supplementary simple blood transfusions.

4. Although recent advances in postpartum management of hæmolytic disease of the newborn have been substantial, the primary problem of antepartum therapy remains unsolved.

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GENERAL PRACTICE

HÆMOLYTIC DISEASE*

G. K. INGHAM, M.D., F.R.C.P.[C.],
Hamilton, Ont.

ONE OF THE COMMONEST and sometimes most puzzling problems encountered by the physician is a patient with an anæmia of which the cause is obscure. Deficiency, marrow depression and blood loss are readily brought to mind as etiological possibilities, but there has been a tendency in the past to neglect consideration of hæmolytic processes as a cause of anæmia. There are several reasons for this. Until fairly recently the etiology and pathogenesis of many of these anæmias was quite obscure, and treatment was consequently not very specific. In addition, their clinical manifestations often tend to be quite subtle and difficult to detect. In the past few years, however, such strides have been made in techniques of diagnosis and treatment that now one can say that a working knowledge of the various factors producing premature destruction of the erythrocyte is not only theoretically interesting but is of great practical importance.

The normal human erythrocyte remains intact in the circulating blood for about 120 days. If, however, the cell is defectively formed, or is subjected to abnormal disruptive influences in its environment, it disintegrates sooner, and a hæmolytic process is said to be present. Thus it may be said that there are two general mechanisms of hæmolysis, one originating in the red cell itself and the other in the cell's environment. These can be quite clearly demonstrated by determining whether the cells in question last a normal length of time when injected into a normal person and, conversely, whether normal cells last a normal length of time in the circulation of a patient in question.

From a practical point of view the first question that confronts us is this: in the clinical and routine laboratory examination of a patient, what findings would lead us to suspect that his erythrocytes are being destroyed prematurely? It should be pointed out here that such findings are based on two simultaneous occurrences: firstly, the more or less sudden release into the blood stream of larger than normal quantities of the products of red blood cell (RBC) disintegration, namely hæmoglobin and red cell debris; and, secondly, the production of anæmia, sometimes with very great rapidity. Some of the important signs which suggest the presence of a hæmolytic process are as follows:

1. Spherocytosis.
2. Spontaneous reticulocytosis (i.e. with no bleeding or hæmolytic treatment).
3. Acholuric jaundice especially associated with dark stools, normal liver and anæmia.
4. Acute anæmia, without hæmorrhage and with chills, back or abdominal pain, red urine.
5. Splenomegaly with any of the above.

The spherocyte is, indeed, the hallmark of the hæmolytic process. It is a small spherical erythrocyte which is thought to result either from a hereditary defect or from injury to the cell membrane. In either case it has, so to speak, the mark of doom upon it. The extent of the spherocytosis usually correlates well with the acuteness of the destructive process. Reticulocytosis simply means that the bone marrow is responding healthily to the stimulus of anoxia (i.e. anæmia). In the absence of hæmorrhage or recent specific therapy in deficiency states it is an indication of blood destruction. Acholuric jaundice is a typical finding when present. The jaundice is rarely intense. In the absence of massive hæmorrhage, acute anæmia points strongly to hæmolysis. The associated chills and fever, back pain, abdominal pain and hæmoglobinuria are due to the products of red cell disruption being released into the blood stream. Splenomegaly in the presence of anæmia is at least suggestive of hæmolytic disease, particularly if the leukocytes and platelets are diminished. The spleen is pre-eminently the erythrocyte "scrap yard", even in health.

Once it has been suspected that a hæmolytic process is present, the next step is to demonstrate that it is. Some of the tests which confirm the presence of premature red cell destruction are listed below.

Absolute

1. The patient's RBC do not survive the usual time in a normal recipient, or normal cells do not survive the normal time in the patient.
2. Hæmoglobinæmia, hæmoglobinuria, hæmosiderinuria.

Relative

1. RBC fragility, osmotic and mechanical. (N.B. increase on incubation.)

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