HAEMOLYTIC DISEASE OF THE NEWBORN: FACTORS AFFECTING THE PROGNOSIS

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As in so many other branches of medicine, South Africa owes a lasting debt to the Institute for Medical Research for its pioneering work in the field of blood groups and blood transfusion. As long ago as 1921 Harvey Pirie[1] published a paper on blood testing before transfusion with a note on the blood-group distribution in the South African Bantu; from 1934 to 1939 Elsdon-Dew[2] was engaged on his large-scale and now internationally recognized investigations on the ABO blood groups of African tribes. His researches were especially noteworthy in that he was one of the earliest workers to employ the statistical approach to the interpretation of blood groups in anthropology. On the clinical side Dr. James Gear, Mr. J. de Bruyne, and their colleagues acted as enthusiastic donors, operators and pathologists in the early days of arm-to-arm transfusion; this was virtually the beginning of blood trans-

fusion in this country and provided the solid foundation on which those who came after have built the existing organizations.

The outbreak of World War II virtually coincided with the discovery of the Rh factor and both these events provided an urgent stimulus to the Institute's researches in blood transfusion; they led directly to the establishment of a blood-transfusion division under the direction of Dr. E. Gaynor-Lewis, a pioneer in this field, and this department carried out the laboratory work for the Rand Blood Transfusion Service which later became the present South African Blood Transfusion Service. Aided by a generous grant from the late Sir Ernest Oppenheimer, a team under Dr. Gaynor-Lewis constructed the first large-scale freeze-drying plant for human serum or plasma, this probably being the only one of its kind, apart from the prototype of Greaves in Cambridge. At the same time a small beginning was being made in the testing of women for the Rh factor, and Altmann and Gaynor-Lewis[3] demonstrated for the first time that only 5% of Bantu were Rh negative as compared with 15% of Europeans. Zoutendyk[4] showed in 1947 that the Rh type cDe, which is present in only about 2% of White persons, is the typical type in the Bantu, among whom it occurs in over 64%, and this has since been recognized as the characteristic Rh type in Africans south of the Sahara.

The records for the month of March 1946, when I returned from working in Britain to assume control of the Institute's blood-transfusion research division, show that 21 women, including 2 Bantu, were investigated for the Rh factor; the figures for December 1962 comprise 1,200 Europeans, 2,500 Bantu and 110 babies. It is the theme of this paper to summarize the conclusions to be drawn from this personal experience during the intervening years and in particular to consider the present-day prognosis in haemolytic disease of the newborn together with some important factors influencing the prognosis. The conclusions will be based on over a quarter of a million antenatal investigations and on a series of 400 consecutive cases of exchange transfusion of babies suffering from haemolytic disease due to Rh or ABO sensitization.

Before the discovery of the Rh factor in 1940 a comparable series of 400 cases of haemolytic disease would have resulted in about 300 deaths and a high proportion of the survivors would have suffered some permanent neurological damage. In the middle and late forties, when treatment consisted of simple transfusion of Rh-negative blood, the mortality would have been reduced to about 100, but the incidence of neurological sequelae would still have been high because the clinical significance of severe icterus was not then realized nor was it amenable to treatment. Since 1951, when a start was made on treating the present series of 400 consecutive cases by exchange transfusion, the mortality has been reduced to less than 5% and the risk of serious neurological complications has been virtually eliminated.

The factors that may influence the outcome either for good or ill may be broadly classified as those largely within the control of the practitioner, those with which the pathologist is mainly concerned, and those, in some respects the most important, that are beyond the control of either and depend mainly on genetics or chance.

It should not be necessary in 1963 to emphasize that every pregnant woman should be tested for the Rh factor and that no Rh-negative female should receive Rh-positive blood; yet both these elementary rules continue to be broken, with disastrous consequences at times. The fact that such negligence has in the United States recently resulted in successful litigation with heavy penalties should serve as a warning to practitioners. Jaundice is another clinical sign that is too frequently neglected; if it appears within the first 24 - 36 hours it should be considered as pathological and warrants urgent laboratory investigation and daily bilirubin estimations until the icteric peak has been reached. There is a risk that neglecting to investigate and treat a severely jaundiced baby which later shows neurological sequelae may be regarded as a culpable omission. Finally, after having the patient tested in early pregnancy the practitioner should follow the pathologist's advice and guidance; in particular it is important to ensure that repeat investigations are carried out where indicated, that the cord blood of all babies of Rh-negative mothers is sent for immediate investigation and, most important, that every woman with antibodies is delivered in one of the larger centres where facilities exist for the prompt investigation and treatment of the baby. In our experience close adherence to the above rules on the part of the practitioner will itself result in significant reduction of mortality and morbidity from haemolytic disease.

The immuno-haematologist and transfusionist can influence the prognosis by advising the practitioner throughout the patient's pregnancy and by having all preparations made, including that of fresh compatible blood, so that an affected baby can be investigated and treated without delay. Close liaison between the practitioner and the laboratory will thus ensure a further significant improvement in the results. Equally important, but largely beyond the control of doctors or patients, are the following factors which can have an important influence on the outcome: Race, ABO incompatibility, sex and body weight of baby, number of former pregnancies, and titre of antibodies.

Influence of race. Since the Rh-negative incidence in the Bantu is approximately one-third that of the Europeans one would expect the incidence of haemolytic disease due to Rh sensitization to be approximately in that proportion; and this is, in fact, found to be the case in practice. The accumulation of very large figures in our department has disproved the prevalent belief and teaching that Rh sensitization is excessively rare in the Bantu. In over 150,000 antenatal investigations in Bantu we have found a sensitization rate of 0·3%; this figure is probably above the true incidence in that there was a certain amount of selection as a result of the referring of some patients from elsewhere because of an abnormal obstetric history. As regards the comparative immunological response between Bantu and Whites we have found that, although in a considerable proportion of cases the condition is equally severe in the two races, a significant proportion of Bantu women remain below the critical antibody level, by our techniques, of 1/16 to 1/32. 115 sensitized Bantu women in a series of 265 failed to reach this titre range and the babies were either not clinically affected or were so mildly affected that an exchange transfusion was not indicated. Many Bantu women with low antibody titres have a

succession of clinically unaffected or mildly affected babies without a significant increase in antibody titre. Possible reasons for this are gradually emerging which point to some fundamental differences in the Rh factor between Bantu and Caucasians; this possibility, which we have stressed for many years, has recently received support from Race and Sanger.[5] Such differences have already been demonstrated by us as far as Rh factor C is concerned.[6]

Influence of ABO incompatibility. It has been known for many years that where wife and husband are compatible on the ABO system, sensitization tends to occur in an earlier pregnancy and the baby is likely to be more severely affected and more likely to require an exchange transfusion. ABO incompatibility between mother and baby has therefore an important sparing effect and it has been calculated that if it were not for this protective mechanism haemolytic disease due to the Rh factor would increase by about 23%. Table I, compiled from our own cases,

TABLE I. EFFECT OF ABO GROUPS ON THE SEVERITY OF HAEMOLYTIC DISEASE

Compatible ABO groups	*% exchanged*
EUROPEANS	
A mothers — A + O babies	94·2
B mothers — B + O babies	92·6
O mothers — O babies	91·1
BANTU	
A mothers — A + O babies	96
B mothers — B + O babies	85·7
O mothers — O babies	86·2
Incompatible ABO groups	*% exchanged*
EUROPEANS	
A mothers — B + AB babies	5·8
B mothers — A + AB babies	7·4
O mothers — A + B babies	8·9
BANTU	
A mothers — B + AB babies	4
B mothers — A + AB babies	14·3
O mothers — A + B babies	13·8

shows the actual group distribution of mothers and babies so severely affected that exchange transfusion was necessary, and emphasizes the dominating role played by ABO incompatibility, not only in reducing the incidence of sensitization but in influencing its severity. This is, of course, a two-edged weapon in that the reduced Rh risk is off-set by an increased risk of ABO sensitization, and as a routine measure we carry out tests for both types of sensitization where the possibility of their occurrence exists.

Influence of sex of baby. It is a generally accepted axiom that under any given set of pathological conditions the survival rate of female babies is significantly higher than that of males. For the 8-year period 1951 - 1958 the South African male:female infant death ratio was 1,325:1,000, while the birth ratio was 1,050:1,000. Table II illustrates the survival rate according to sex in 400 of our cases of haemolytic disease treated by exchange transfusion. The combined figures for Europeans and Bantu show that the mortality rate among males is almost twice that of females. The ratio of males to females susceptible to treatment was 843:1,000, and it is tempting to theorize

TABLE II. RESULTS OF EXCHANGE TRANSFUSION ACCORDING TO SEX OF BABY

	Total transfused	*Died*	*Mortality %*
European males ..	121	12	9·9
European females ..	156	9	5·8
Bantu males	62	6	9·7
Bantu females ..	61	3	4·9

that the greater risk to males exists also *in utero* with an increased male foetal loss due to intra-uterine deaths. Walker and Mollison[7] have also noted that in a series of infants dying of kernicterus males were twice as numerous as females.

Influence of body weight. The influence of body weight on survival after exchange transfusion is illustrated in Table III. One frequently quoted objection to premature induction of labour in Rh sensitization is that the salvage of live babies is offset to some extent by the loss due to prematurity. We ourselves have constantly recommended induction at 37 - 38 weeks, and that this does not result

TABLE III. INFLUENCE OF BODY WEIGHT ON RESULTS OF EXCHANGE TRANSFUSION

	2-3 lb.		*3-4 lb.*		*4-5 lb.*		*5-5½ lb.*	
	Lived	*Died*	*Lived*	*Died*	*Lived*	*Died*	*Lived*	*Died*
Europeans	1	0	4	1	16	5	21	4
Bantu	0	0	3	1	6	2	13	2
Total	1	0	7	2	22	7	34	6

15/79 died

	5½-6 lb.		*6-7 lb.*		*7-8 lb.*		*8 lb. and over*	
	Lived	*Died*	*Lived*	*Died*	*Lived*	*Died*	*Lived*	*Died*
Europeans	23	2	113	5	55	6	14	0
Bantu	14	0	43	2	32	0	12	0
Total	37	2	156	7	87	6	26	0

15/321 died

	Total
European	270
Bantu	130
	400

in the birth of premature babies is shown by the fact that only 20% weighed less than 5½ lb., which is not significantly different from the proportion among normal mothers delivered spontaneously. The small babies in our series were truly premature in that they were born spontaneously before 37 weeks. The mortality among premature babies was 4 times that among the mature while no deaths occurred among babies weighing over 8 lb.

Influence of number of pregnancies. Provided that a patient has never received Rh-positive blood by any route, sensitization in a first pregnancy is virtually unknown; most Rh-negative patients do not produce antibodies at all, but an analysis of 500 consecutive sensitized patients shows that of those destined to produce antibodies, 40% will do so in their 2nd pregnancy and 33% in their 3rd (Table IV).

TABLE IV. PREGNANCY IN WHICH ANTIBODIES WERE FIRST DEMONSTRABLE

1st	*2nd*	*3rd*	*4th*	*5th*
14	218	165	64	19
6th	*7th*	*8th*	*9th*	*Total*
11	5	3	1	500

Chances of survival. The factors influencing the prognosis having been described, it remains to consider how these have worked out in practice. It is now accepted that with proper antenatal care and prompt investigation and treatment of the baby the risk of neurological sequelae is negligible. Survival therefore means the survival of a normal child and the figures illustrated in Table V summarize our results in a series of 400 cases treated over a period of 10 years. The

TABLE V. RESULTS OF EXCHANGE TRANSFUSION OF 400 BABIES

	Number	*Survived*	*Died*	*Mortality* %
Europeans	265	244	21	7·9
Bantu	135	126	9	6·7
Total	400	370	30	7·5

COMPARATIVE FIGURES

Newcastle, England 1948–1957*a* ..	652	605	47	7·2
Western Australia 1951–1954*b* ..	164	150	14	8·2
Sydney, Australia 1950–1960*c* ..	223	194	29	13·0
USA 1953–1958*d* ..	519	481	38	7·3
USA 1949–1961*e* ..	285	251	34	11·9

a. Walker, W. (1958): Vox Sang. (Basel), **3**, 336.
b. Kelsall, G. *et al.* (1957): Lancet, **2**, 1255.
c. McBride, W. G. (1961): Med. J. Aust., **1**, 403.
d. Boggs, T. R. J. and van Westphal, M. C. (1960): Pediatrics, **26**, 745.
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mortality is increased by the inclusion of cases referred late for investigation and treatment, but is about 4% in patients investigated by our services and treated according to our pre-arranged advice and plans. We recently completed a series of 100 consecutive cases without a death.

Compared with the representative overseas figures shown our results are very gratifying, especially when it is remembered that the exchange transfusions were carried out as a 24-hour service by one team in 25 different hospitals and maternity homes spread over a radius of 45 miles. It is felt that no further significant reduction is possible and before embarking on a further pregnancy sensitized patients should reconcile themselves to a 2 - 4% risk of neonatal death and a 12 - 15% risk of stillbirth if the antibody titre is high. Foetal loss due to stillbirths remains the crux of the Rh problem and no practical solution to this aspect is to be anticipated in the foreseeable future. For this reason we consider further pregnancies to be contraindicated where the husband is homozygous Rh-positive and the wife has been sensitized, especially if such sensitization has been partly due to an incompatible blood transfusion in the past and if the titre is high.

SUMMARY

A brief review is given of the part played by the South African Institute for Medical Research in blood-group research and blood transfusion.

Our experience of haemolytic disease of the newborn is analysed and some conclusions are drawn from the investigation of more than 250,000 European and Bantu patients and the exchange transfusion of 400 babies.

The influence on prognosis of race, ABO blood groups, sex and weight is described.

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