'HAEMOLYTIC' JAUNDICE OF THE NEWBORN (NOT Rh) IN PAEDIATRIC WARDS OF GENERAL HOSPITALS*

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In 1969 the concept of neonatal jaundice no longer conjures up ideas of 'physiological' jaundice or of rhesus incompatibility as the main aetiologies. The antenatal clinics should have removed most of the possibilities of congenital syphilis. In up-to-date communities where the mothers' bloods are checked for Rh and ABO grouping and for blood-group antibodies during pregnancy, and where all mothers with potential troubles of that kind are delivered in special units where their course can be most carefully supervised, one might suppose that neonatal jaundice would no longer be a major problem. But it still is a considerable one, and although the standard treatment—replacement transfusion—is quite successful in a general way, there is evidence that makes one wonder why it should be; are we not perhaps blindly applying the same treatment to a number of conditions which really need entirely different therapy?

Pyogenic infection has often, without very clear justification, been blamed for haemolytic jaundice of uncertain origin in the neonate. Absorption of bilirubin from an enclosed haemorrhage, such as cephalhaematomata, has also been indicted for many years. More recently, Rh incompatibility, followed thereafter by ABO incompatibility, thyroid deficiency, inclusion-body infections, glucose-6-phosphate dehydrogenase deficiency, metabolic disorders and, most recently, lack of glucuronyl transferase, have all been added to the list of possibilities. The only helpful therapeutic suggestion, which is really prophylactic in nature, is the development of anti-D serum for use in non-sensitized, Rh-negative mothers after delivery of an Rh-positive child. It is not yet available in material amount and is almost prohibitively expensive, at R45 per dose.

To give all these infants replacement transfusions is also expensive in money and time, and the fact that even after the third replacement the unconjugated bilirubin may be still at about the same level as it was before the first one, makes the rationale of the treatment very doubtful. There is no other definite means of removing the unconjugated bilirubin from the circulation, though tests are at present being carried out on the possibilities of mopping it up with albumin, as are the use of ACTH, exposure to ultraviolet irradiation, and attempts to increase the glucuronyl transferase by giving the child oral nikethamide or phenobarbitone.

It is obvious that the situation, as regards both aetiology and treatment, is far from satisfactory and that more information is needed. It was with the idea of possibly clarifying the position in Cape Town that the present investigation was undertaken.

ANALYSIS OF CASES

The 33 infants in whom the jaundice was accepted as being due to Rh incompatibility have not been included in the figures given in this paper, except in Table II. The infants were all those cases of neonatal jaundice, presumably haemolytic because all had an unacceptably high level of unconjugated bilirubin, admitted to the general paediatric wards of the Red Cross and Groote Schuur Hospitals over the years 1960 - 1967 inclusive. They were all born at home, many in the most unsalubrious circumstances, and in many instances the child's mother never appeared at hospital at all. This is the main reason why there is much, really vital, information missing. The difficulties of establishing accurate or even intelligent communication with some of the people who conducted the children to and from hospital—if they were not simply 'dumped' by an ambulance which also brought a letter from a Coloured or Bantu midwife, in a language strange to her—account for many of the information gaps. But enough data are available about 387 neonates over the 8-year period to justify a review of the situation.

Table I contains all the records of so-called 'physiological jaundice', together with any other labels attached to these records. There was no incontrovertible proof of the real reason why these babies were jaundiced. Table II shows the cases of Rh incompatibility in the general paediatric ward records; for comparison, 387 other haemolytic anaemias were found over the same period. It is obvious that the Rh group is relatively insignificant in general paediatric practice.

TABLE I. UNIDENTIFIED ICTERUS NEONATORUM, 1960–1967

Condition	*No.*
Prematurity	24
Umbilical sepsis	28
? Generalized infections	69
Toxoplasmosis by laboratory test	4

TABLE II. ERYTHROBLASTOSIS (Rh), 1960–1967

	White	*Coloured*	*Bantu*	*Total*
No. of cases	18	14	1	33

Fig. 1, derived from figures obtained by McDonald[1] in 1964 on healthy infants who had uncomplicated births and whose bilirubin levels were assessed in the same laboratories as those in this paper, is included to show the local idea of the range of 'normal' figures. The mean in each of the five groups of 15 is shown to be from 3·1 to 6·1 mg. and the scatter from 0·5 to 14·3 mg. This would probably be acceptable anywhere as the physiological range for total serum bilirubin in the neonate.

The numbers of the infants now under consideration are shown for each successive year in Table III. The vast majority are Coloured (80%) with small numbers (10% of each) of White and Bantu. (The proportions of all inpatients in these years are White 29%, Coloured 58% and Bantu 13%.) There is a surprising preponderance of males, and a very large number of infants who were premature by weight on admission. If the child was not admitted on the first or second day of life, or if its weight

*Based on a paper presented at the 8th Congress of the South African Paediatric Association (M.A.S.A.), Cape Town, September 1968.

TABLE III. HAEMOLYTIC NEONATAL JAUNDICE (NOT Rh), 1960–1967

Year	No. cases	Race			Sex		Premature	Deaths	Kernicterus
		W	C	B	M	F			
1960	21	5	15	1	15	6	2	3	? 1 (bil. 45, day 4)
1961	20	5	13	2	12	8	4	2	? 1 (cerebral birth injury)
1962	28	1	22	5	19	9	6	4	? 3 (bil. 14, 15, 28)
1963	64	6	55	3	36	28	13	2	—
1964	45	4	37	4	28	17	7	3	1 (bil. 35, day 4)
1965	48	3	39	6	30	18	5	2	? 1 (bil. 30, day 10)
1966	67	7	52	8	46	21	22	3	4 (bil. 34, 33, 32, 27)
1967	94	7	75	12	60	34	38	2	1 (bil. 27, day 3)*
Total	387	38	308	41	246	141	97	21	?12

W = White; C = Coloured; B = Bantu; bil. = total bilirubin

*Confirmed at postmortem examination.

was not far below 5 lb. when admitted at a greater age, it was not considered to be premature on a weight basis. The death rate was gratifyingly small. The number of instances of kernicterus is doubtful as 'follow-up' is poor; only one was confirmed at autopsy and at least one other might have had a cerebral birth injury.

Fig. 2 shows a sample of the scatter of serum bilirubin levels found in the infants discussed in this paper.[2] Fifty-three of the 64 patients recorded for 1963 are compared with the criteria for replacement transfusion suggested by Allen and Diamond.[3] It is obvious that only 14 of the 53 were below Diamond's danger-line and half of these were not transfused. The premature infants were all, except one, apparently in grave danger; only one had a bilirubin of less than 15 mg. and one was on the 32 mg. level and apparently escaped undamaged. Although these are total bilirubin figures, the conjugated fraction was usually in the range of 1 - 3 mg. and its subtraction from the total would have made little difference.

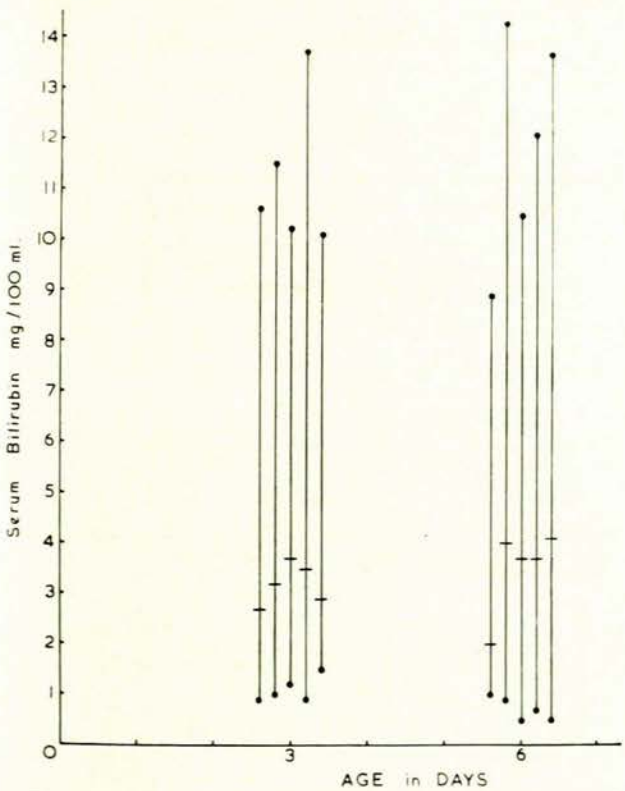

Fig. 1. Range and mean of bilirubin levels in 75 normal neonates at 3 and 6 days of age.[1]

Table IV shows that, if the histories of the time of the alleged onset of jaundice can be regarded as even approximately correct, there was probably considerable delay after its appearance before the child was brought to hospital. By the third day of life 288 were said to be jaundiced and 281 had been seen at hospital by the fifth day. This cannot be taken as a point of differentiation from the Rh type of jaundice, since more than a third of them were said to have been jaundiced to a considerable degree within 24 hours of birth. We do teach that jaundice within the first 24 hours must be regarded as Rh disease until proved otherwise, but it is quite difficult to detect this colour change in a pigmented skin and in a bad light and very many of these infants were being cared for at home by untutored people. Nor does the order of birth help in differentiation of the type of jaundice; similar numbers of infants were affected in the first, second and third pregnancies (Table V). This is not the picture one

TABLE IV. TIME OF ONSET OF HAEMOLYTIC NEONATAL JAUNDICE (NOT Rh)

	Day of life admitted									
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
No. admitted	49	47	51	78	56	33	24	10	9	9
No. whose jaundice appeared on day shown above	101	106	81	30	15	5	3	2	1	4

The above details were not recorded in every case, hence some discrepancy in numbers.

TABLE V. PARITY AS RELATED TO HAEMOLYTIC NEONATAL JAUNDICE (NOT Rh)

	Parity									
	1	2	3	4	5	6	7	8	9	10
No. of infants in each order of pregnancy	42	40	39	24	30	24	21	5	6	6

The above details were not recorded in every case, hence some discrepancy in numbers. More than 10 was quite common, up to 23 pregnancies having been recorded.

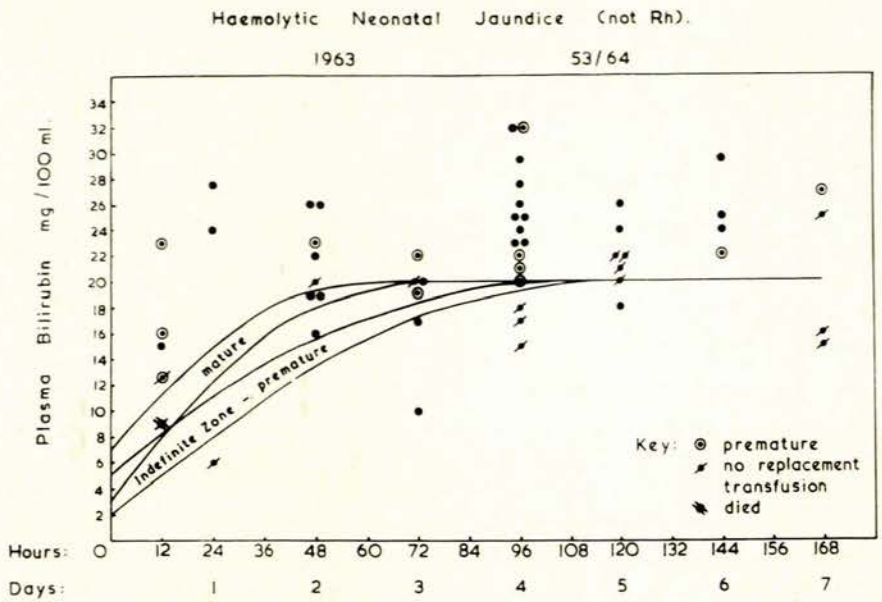

Fig. 2. Serum bilirubin levels in 53 of the 64 infants recorded for 1963.

would expect if Rh incompatibility was really a large factor in the aetiology of these undetermined cases of jaundice, and this evidence supports the figures given in Table II.

Table VI presents consideration of the blood groups of infant and mother where this was known. Of 282 such

TABLE VI. BLOOD GROUPING OF INFANT AND MOTHER

	No. of cases
Potential Rh incompatibility	47
Potential ABO incompatibility	138
Inexplicable (same ABO and Rh groups, or O in baby and same Rh groups)	97
Total	282

couples, 235 had the same Rh grouping in mother and child. Only 47 pairs showed that a possible Rh incompatibility might have been present, but the direct Coombs test (D) was negative in 41. In the whole series a considerable number of Coombs tests were not recorded. Of the 235 pairs, 97 either had identical ABO grouping in mother and child or the infant belonged to group O and was identical with its mother in Rh typing. These 97 are classed as 'inexplicable', on a blood-group basis, though it is realized that this may not be absolutely correct since the more unusual blood groups are not always considered. The remainder, 138 (49%) of the 282, were possibly ABO incompatible. The Coombs test was singularly unhelpful. In New York[4] it is said to be positive in the presence of an ABO incompatibility as well as in Rh incompatibility. In the present series 293 of these tests were recorded. Only 32 infants showed a direct positive and six of these were in the 'inexplicable' group.

Enquiry into some of the other possible causes of neonatal jaundice is shown in Table VII. It appears that a negligible number could be attributed to syphilis. Sepsis, mostly of the umbilicus, and positive blood cultures—*Staph. aureus*, coliforms, proteus, enterococci—obviously deserve close attention. Deficiency of glucose-6-phosphate dehydrogenase is clearly worth closer scrutiny but neither toxoplasmosis nor inclusion bodies show impressive figures. Toxoplasmosis was evident only on blood testing, never clinically. No abnormal haemoglobins were found in the few instances where they were sought.

The haemorrhages were mostly cephalhaematomata or intracranial. The haemoglobin levels in these babies did not suggest any serious loss of the circulating blood, and the importance of haemorrhages cannot be assessed. The Departmental records for the same years show 58 cephalhaematomas without neonatal jaundice and it is a relatively common occurrence in obstetric units without causing any other trouble.

Keet *et al.*,[5] in 1966, came to the conclusion that in almost half of their series of children with hyperbilirubinaemia (74/164) no definite cause for the abnormality could be found. They had excluded prematurity from their series. In the present series in which premature infants made up nearly a quarter of the total number, about one-third of the high bilirubin levels could not be explained—97 of the 282 (Table VI) where enough detail was recorded.

The possibility that prematurity by itself might be intimately associated with the kind of neonatal jaundice under discussion calls for comparison of the premature and non-premature sections of this series of cases. The pertinent figures are shown in Table VIII. These are given as percentages of the numbers of children whose records give the appropriate information, and the actual numbers of these are included for each grouping. About a quarter of each group, premature and non-premature, were admitted in the first two days of life. This is not the usual finding in blood-group incompatibility where much larger numbers would be expected. Twice as many prematures, proportionately, were first babies but even in them this might explain only a quarter of the total, e.g. on the basis of gross immaturity of the liver. Jaundice was noticed on the first day in a smaller proportion of the premature infants, which suggests that, if the jaundice is due to an enzyme deficiency, the defect is greater in infants born at

TABLE VII. POSSIBLE AETIOLOGICAL FACTORS INVESTIGATED

	Pos.	*Neg.*	*Incidence in cases checked*
Blood Wassermann reaction	3	167	1·7%
Blood culture	22	94	19%
*G-6-PD deficiency	10	49	20%
Doubtful	2		
Toxoplasmosis (dye)	4	41	9%
Inclusion bodies	—	19	—
Abnormal haemoglobin	—	4	—

Haemorrhage present in 37 cases
Sepsis present in 18 cases
? Hepatitis present in 3 cases

*As judged by Motulsky test.

TABLE VIII. COMPARISON OF PREMATURE AND FULL-TERM INFANTS

	Premature (total 98)		*Full-term (total 289)*	
	No. investigated	*% of those investigated*	*No. investigated*	*% of those investigated*
Age at admission	98		289	
Day 1		17		11
Day 2		6		14
Day 3		10		14
Pregnancy order	63		183	
1		28		13
2		11		18
3		5		19
Jaundice noticed	88		265	
Day 1		23		30
Day 2		21		32
Day 3		30		20
Potential incompatibility	55		224	
Rh		7		15
ABO		46		49
None		46		31

term than in those born prematurely, and this seems most unlikely. Moreover, it is common knowledge that the levels of conjugated bilirubin are comparable in the two groups. Complete absence of any blood-group incompatibility was found in a considerable proportion of both categories, though this was not exhaustively checked. In view of these findings there does not seem to be much justification for regarding premature infants' jaundice as materially different from that of any other group of neonates.

Replacement transfusion, in quantity equal to twice the estimated blood volume, was not very satisfactory and had to be done two and three times because of rebound of the bilirubin level to its original height. This seems to support the suspicion that Rh or ABO incompatibility of the cells is not always, or even often, the cause of the trouble. Recently a premature baby weighing 3 lb. had 6 exchange transfusions, every 12 hours for 3 days, and the total bilirubin at the end of that time was almost the same as at the beginning—34 mg. as compared with 37 mg. This makes no sense at all. It does, however, indicate continued production of bilirubin which was not being conjugated or excreted.

Fig. 3 illustrates a common experience. This child, weighing 6 lb. 8 oz., was admitted on the third day of life with a history of jaundice for 24 hours. This was the mother's seventh pregnancy, the first 4 children being normal; the next 2 were both severely jaundiced and died on the fifth and third days respectively. The mother's blood was known to be group O positive, with negative indirect Coombs and Wassermann reaction tests. There is no information available about the father. The patient was group B positive and had negative direct and indirect Coombs tests, a haemoglobin level of 15·6 G/100 ml. and a reticulocyte count of 22%. The bilirubin levels are shown in Fig. 3. Group O Rh-negative blood was used in all the transfusions. Albumin was added to the second transfusion. There was trouble with the third transfusion, which was abandoned, and only after the fourth one did the bilirubin settle below the 20-mg. level. The baby was sent home, apparently well, on the seventh day of life. This child was tested for the aetiological factors mentioned in Table VII, with negative results, and was given ampicillin as a safety measure. He was in serious danger of cross-infection throughout his entire stay in hospital and his response to treatment could not possibly

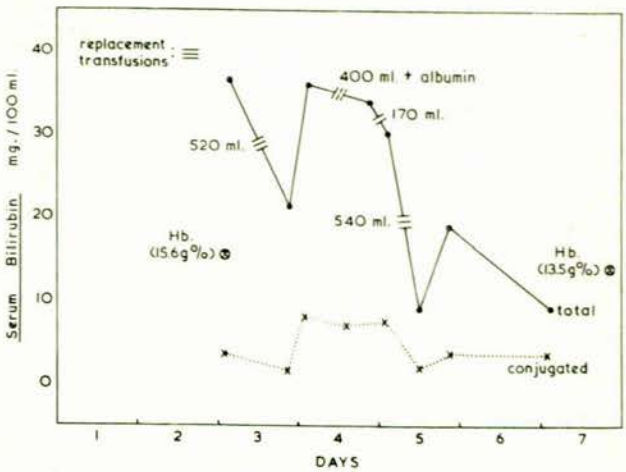

Fig. 3. Serum bilirubin levels in relation to treatment in neonatal haemolytic anaemia as discussed.

be described as immediate. It took 48 hours, 4 transfusions, 1,600 ml. of blood, and intravenous albumin, plus an antibiotic merely to allay anxiety on his behalf.

The only conclusion that can be drawn from these observations is that we still do not know the cause of a very large proportion of the cases of neonatal jaundice which come through our hands. That most of them are not due to Rh incompatibility seems to be indisputable. The development of a potent anti-D substance will therefore have very little effect on the incidence of this jaundice, though it will be of inestimable value where there is mother-child Rh antagonism. The very large remaining number of neonates jaundiced to a degree which provokes anxiety about their future will still remain to be dealt with and, from the data given above, it is obvious that much research is still needed to elucidate the cause of their jaundice and to find some form of treatment or prophylaxis applicable to them. There is little ground for complacency or for belief that the present line of attack is the ultimate.

SUMMARY

The major problem in the Cape Town area in neonatal jaundice appears not to be associated with Rh incompatibility. There is urgent need for more haematological information on this subject and, somehow or other, the mother's blood must be obtained for examination when these infants are sent for assessment. Some way of increasing the conjugation of bilirubin in the neonatal period is needed.

The Coombs test, as applied at present, is not a reliable index of the presence of Rh incompatibility or of the need for replacement transfusion when the level of unconjugated bilirubin has risen above the accepted 'safety level'.

The influence of infection and glucose-6-phosphate dehydrogenase deficiency in producing neonatal jaundice requires closer investigation but at present neither seems to play a major role in the aetiology which, in a large number of infants, remains obscure.

Replacement transfusion is probably being used excessively but at present there does not seem to be a better alternative.

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