THE PATTERN OF HAEMOLYTIC DISEASE OF THE NEWBORN

BY

BARBARA S. DAVIES, JOHN GERRARD, and J. A. H. WATERHOUSE

From the Departments of Paediatrics and Child Health and Medical Statistics, University of Birmingham

(RECEIVED FOR PUBLICATION JULY 8, 1953)

Maternal immunization against the Rh factor may result in intra-uterine death of the foetus or hydrops foetalis, which we have called severe forms of the disease, or in icterus gravis, with or without kernikterus, or a haemolytic anaemia without obvious jaundice, and these we have called mild forms of the disease. It is frequently assumed that in any one family successive Rh-positive infants tend to be progressively more severely affected (Allott, 1951; Diamond, 1950; Ellis, 1951; Salomonsen, 1952; Sheldon, 1951; Whitby and Newns, 1953) and though this is sometimes true it is not entirely in accord with our experience. In most of the families we have studied, the affected offspring have all been mild cases, but in other families they have all been severe cases; a small proportion of families have contained cases of both kinds. This concentration of the severe cases into a small proportion of the families is well illustrated in a consecutive series of 103 'Rh families' at the Birmingham Maternity Hospital, in which four-fifths of the severe cases occurred in only one-fifth of the families. By contrast in the whole of the material at our disposal more than three-quarters of the families contained no severely affected case.

Material

Our material has been drawn from several sources: from the Birmingham Maternity Hospital, from the maternity department of Dudley Road Hospital together with other maternity hospitals in Birmingham where replacement transfusions have been performed in the last three years, and from the Birmingham Children's Hospital. We have studied 440 families made up as follows:

Birmingham Maternity Hospital. From 1949 to 1953, 103 families, in which Rh iso-immunization had occurred, formed a consecutive series, whether the infant was viable at birth or not.

Dudley Road and Other Maternity Hospitals. From 1950 to 1953, 114 families, not consecutive, were selected by the fact that in nearly every family

one infant had been given a replacement or simple transfusion.

Birmingham Children's Hospital. From 1927 to 1953, 223 families, in which at least one child had received treatment for haemolytic disease at the Children's Hospital were studied.

Method of Study

The families in each group have been sub-divided into those 'mild' families in which the first child affected with haemolytic disease was a mild case by our definition, i.e., icterus gravis (with or without kernikterus) or haemolytic anaemia, and those 'severe' families in which the first affected was stillborn or hydropic, classed as severe forms. The incidence of the mild and severe forms of the disease in infants born subsequently has then been analysed, and the details of this analysis are presented in Table 1. We have in this table assumed that every stillbirth was due to Rh iso-immunization. We have classified as miscarriages and abortions all deliveries before the twenty-eighth week of pregnancy; the higher incidence of these in the severe group of families suggests that some at least may have been due to Rh iso-immunization.

Results

It is evident from Table 1 that the three mild groups all show a similar pattern. Thus, if the first affected child is a mild case, the ratio of mild to severe among subsequent children is 9 to 2. The three severe groups, however, are not so homogeneous and this was not unexpected: the Birmingham Maternity Hospital cases are an unselected consecutive series, the Birmingham Children's Hospital are predominantly mild cases because of the selection of families including at least one mild case, and the Dudley Road and other maternity hospitals cases form an intermediate group. Of these three, therefore, the Birmingham Maternity Hospital cases are probably the most reliable on which to base

prognosis, whence, if the first affected is a severe case, the ratio of mild to severe among subsequent pregnancies is 1 to 2. Thus the chances that the next affected will be a severe case are considerably greater if the first is a severe case than if it is mild.

Two further considerations, each tending to decrease the number of subsequent severe cases in the severe group, must be taken into account.

(1) Some families belonging more properly perhaps to the mild group are classed as severe on an early stillbirth possibly not due to Rh iso-immunization; to this we have already referred as deliberate policy.

(2) In some women, already known to have produced Rh stillbirths, pregnancy has been induced early with the production of a viable child with no more than a mild form of the disease. In an attempt to eliminate bias due to these circumstances we have selected 15 families in which the first affected was hydropic or stillborn and known to be due to Rh iso-immunization. Of subsequent offspring delivered at term, two were unaffected (Rh negative), two were mildly and 19 were severely affected. The ratio of mild to severe is now 1 to $9\frac{1}{2}$, or in these families, of viable to non-viable in pregnancies subsequent to a known 'Rh severe' case, 2 to $9\frac{1}{2}$, almost exactly the inverse of the ratio found in 'mild' families.

Table 1 shows that the differences in the average number of children per family between the six groups are not very great, although in computing these figures we have included as 'children' all those pregnancies terminating in stillbirths or abortions, in addition to live births. But when the total is analysed into the mean numbers before and after the first affected, it will be seen that 'severe' families have on an average from two and a half to three times as many children after the first affected as do 'mild' families; in fact, 64% of the 'mild' families have no further children after the first affected, com-

pared with 16% of the 'severe' families. In the remaining 'mild' families, however, 83% of the next pregnancies to the first affected and 60% of the next but one, produced mildly affected children, the corresponding figures for severe families being 43% and 56%. The last figure may be somewhat inflated because of the inclusion of several children born after premature induction of labour: in the 15 selected families referred to above, the percentages of mild cases in the next and the next following pregnancies are only 20% and 0% (five cases only) respectively.

This confirms our original suggestion that one group of mothers tends to have infants with mild forms of the disease and that even their second and third affected are predominantly mild, while the other, smaller group of mothers tends to have severely affected infants. Allen, Diamond and Vaughan (1950) have stated that of second affected infants 40% are stillborn, which would suggest that there is a rapid increase in the severity of the disease in successive affected offspring. This increase, however, is more apparent than real because it is the severely affected mothers, rather than the mildly affected, who are most productive. That 'severe' families in general have nearly three times as many subsequent pregnancies as 'mild' families accords with the common obstetric experience that a succession of stillbirths acts more as a stimulus than a deterrent in many families eager for living children of their own.

Possible Aetiological Factors

Table I shows the additional and important fact that severely affected mothers have fewer children than mildly affected mothers before their first affected child. From this we may surmise that severely

TABLE 1
AN ANALYSIS OF FAMILIES ACCORDING TO THE SEVERITY OF THE DISEASE IN THE FIRST AFFECTED CHILD

CHILDREN OF MOTHERS WITH PREVIOUSLY AFFECTED CHILDREN													
Hospital Group	No. of Families	Previous Pregnancies*	1st Affected	Subsequent Children					Total Children	Children per Family			
				Total No.	Affected		Normal (%)	Miscellaneous and Abortions (%)		Average No. per Family	Children before 1st Affected	Children after 1st Affected	
					Mild (%)	Severe (%)							
Mild	B.M.H.	80	181	80	60	70.0	21.7	5.0	3.3	321	4.01	2.26	0.75
	O.M.H.	99	198	99	38	73.7	15.8	7.9	2.6	335	3.38	2.00	0.38
	B.C.H.	197	413	197	165	67.8	12.2	13.9	6.1	775	3.93	2.10	0.84
Severe	B.M.H.	23	29	23	42	23.8	47.6	7.1	21.4	94	4.09	1.26	1.83
	O.M.H.	15	27	15	39	33.3	30.8	23.1	12.8	81	5.40	1.80	2.60
	B.C.H.	26	35	26	54	55.6	16.7	16.7	11.1	115	4.42	1.35	2.08

* Including miscarriages and abortions (i.e. all deliveries before 28th week of pregnancy).

B.M.H. = Birmingham Maternity Hospital.

O.M.H. = Dudley Road and other maternity hospitals.

B.C.H. = Birmingham Children's Hospital.

affected mothers are more readily sensitized than mildly affected mothers, and this susceptibility to sensitization results in the earlier onset and greater severity of the disease in this group.

We have also investigated the incidence and distribution of several other serological properties:

The Titre of Rh Antibody in the Maternal Blood.

This was known in 142 deliveries (94 mild and 48 severe), and is shown diagrammatically in Fig. 1. Low, intermediate and high titres may be associated with any mani-

festation of the disease, with the exception that we found titres above 1 in 512 only when the foetus was hydropic, stillborn or, more remarkably, Rh negative. It seems likely that the titre may rise excessively when the foetus is unable to adsorb antibody (Arnold, Walsh and Herzger, 1951), i.e. when it is dead, saturated (hydropic) or Rh negative.

Non-Homologous Rh Blood Transfusions to the Mother. The incidence of these was analysed only in the Birmingham Maternity Hospital and Dudley Road and other maternity hospitals groups where our data were adequate, and the results are shown in Table 2.

TABLE 2
INCIDENCE OF RH-POSITIVE BLOOD TRANSFUSIONS
SENSITIZING RH-NEGATIVE MOTHERS

	Mild	Severe
Total number of mothers	179	38
Number transfused with Rh-positive blood	14	11
Percentage receiving transfusions of Rh-positive blood	7.8	28.9

The proportion of mothers in the severe group who had been transfused with Rh-positive blood is more than three times that found in the mild group. This is a highly significant difference, and it seems

FIG. 1—The maternal antibody titre near term in 94 mildly and 48 severely affected infants.

therefore that such transfusions may sometimes dislodge a woman from the mild to the severe group, but this factor accounts at the most for not much more than a quarter of the cases in the severe group.

The ABO Groups of the Parents. The parents of children with haemolytic disease are compatibly mated on the ABO system more frequently than would be expected (Levine, 1943), i.e. if the Rh grouping were to be ignored, the father could be a donor to his wife in more instances than would occur in random matings. The distribution of the known ABO grouping in our cases is shown in Table 3.

TABLE 3
THE PERCENTAGE DISTRIBUTION OF ABO GROUPS IN
PARENTS AND AFFECTED OFFSPRING

ABO Group	Mother		Father		Baby	Normal Distribution
	Mild	Severe	Mild	Severe		
O	36.1	32.4	51.8	68.7	42.7	46
A	51.6	56.8	44.6	25.0	45.2	43
B	8.2	10.8	3.6	6.3	8.1	9
AB	4.1	0	0	0	4.0	3
Total	122	37	83	32	124	

The distribution of the ABO groups in affected infants does not differ appreciably from that in the population at large, but there is a shift towards

Group A in the mothers and towards group O in the fathers, i.e. towards compatibility in the above sense. This shift is greatest in the severe group, but it is still obvious in the mild group and by itself does not explain, though it may influence, the incidence of the two groups. Stated in another way, nearly 87% of the fathers, if the Rh group is ignored, could be blood donors (cells to serum) to their wives, while only 61% of the wives could be donors to their husbands (Table 4). The proportion of wives able

both the mild and severe groups, from which we may infer that whatever agency determines the character of the disease in a family it is not closely related to the D-genotype of the father. Also shown in Table 6 is the overall proportion of homozygous (DD) Rh-positive fathers expected in our material, calculated from our family size distribution and Table 5. There is a slight excess of homozygous fathers over the expected figure which may be due to the inclusion of some pregnancies on serological grounds rather than in the way postulated in Table 5.

TABLE 4
ABO COMPATIBILITY OF PARENTS

Compatibility	Mild Group (%)	Severe Group (%)	Combined (%)	General Population (%)
Husband to wife ..	87.5	84.4	86.6	66.2
Wife to husband ..	66.3	46.9	60.7	66.2
Total numbers	80	32	112	

to give blood to their husbands is in close agreement with expectation in the mild group but differs considerably, though not quite significantly, in the severe group.

The Parental Genotype. In an unselected group of Rh-positive individuals approximately 43% are homozygous (DD) with respect to the D antigen, but the proportion is greater among the fathers of babies with haemolytic disease. The actual proportion to be expected depends upon the distribution of family size, and Table 5 shows the ratios calculated on the assumption that the second and subsequent Rh-positive foetuses will be affected. Among families with two children with haemolytic disease the expected ratio of homozygous to heterozygous fathers is about 3:1 (Fraser Roberts, 1951, quoted by Race, 1952), but in families with three children it is 3:2, and thereafter the proportion of homozygotes decreases towards the general population values.

TABLE 5
D-GENOTYPE OF RH-POSITIVE FATHERS OF FAMILIES WITH HAEMOLYTIC DISEASE

Size of Family	Homozygous % Expected
2	75
3	60
4	52
5	48
6	45.7
7	44.4
8	43.6
General Population	42.8

In our material Table 6 shows that the ratio is about 2:1, and, moreover, it is almost identical in

TABLE 6

	Homozygous (%)	Heterozygous (%)	Total Number
Mild	63.6	36.4	110
Severe	69.7	30.3	33
Expected ¹	57.1	42.9	

Discussion

On the evidence we have presented there seems reasonable justification for the division of families with haemolytic disease into two main groups. The offspring of one are predominantly mildly affected, those of the other are predominantly severely affected, but there are also some intermediate families in which the disease in successive affected infants is more severe. Our analysis has probably emphasized the two extremes of a spectrum.

From the data we have collected it is not possible to predict into which group a woman will fall, but the division into two groups based on the form which the disease takes in the first affected offspring is of prognostic value. If a mother's first affected infant is a mild case, then in 83% of cases her next child will also be mildly affected. The danger of kernikterus can almost always—if not always—be obviated by adequate exchange transfusions (Diamond, Allen, Vann and Powers, 1952) and our own experience (Davies, Gerrard, Hatchuel and Howarth, 1953). But if the first affected child is a severe case the next affected will, in 80% of cases, also be a severe case, if delivered at term. It seems reasonable in these cases (unless the father is heterozygous) to practise the premature induction of labour. This has been done in 10 of our families (11 pregnancies, including one twin pregnancy) and in every case the baby was mildly affected. Induction or Caesarean section has been carried out as early as the thirtieth week, but was usually performed between the thirty-fourth and thirty-sixth weeks of pregnancy. Such a transformation in the outlook for the foetus is not to be

expected every time, but from our material it seems that induction or Caesarean section at the thirty-fifth week might have saved three-quarters of the infants in this severe group (19 out of 25 cases).

The decision when to induce in the individual case can only be taken by the obstetrician, but he may be guided by the mother, who may notice that foetal movements are becoming less vigorous (Watson, 1953), and by the liquor, a rise in the non-haematin iron content being associated with a corresponding anaemia in the infant (Bevis, 1952). When the baby is delivered, either by the natural route or by Caesarean section, and if it has haemolytic disease, it is important that the paediatrician should be prepared to attempt an adequate exchange transfusion (80-100 ml. per lb. body weight) soon after delivery, or to give two smaller exchange transfusions (60 ml. per lb. body weight) should the baby's condition not allow the larger initial exchange. Both lines of treatment have been used with encouraging results.

We are unable to state why there are these two groups, but there are two factors which suggest that the severity of the disease in the infant or foetus is related to the efficiency of the maternal production of antibody. First, the women who have the fewest unaffected infants, and who are presumably the most easily sensitized, are those who have the most severely affected infants, and secondly, the Rh-negative women who have had transfusions of Rh-positive blood, a very powerful antigenic stimulus, also tend to have severely affected infants. It is nevertheless true that the maternal titre of antibody does not clearly reflect the severity of the disease in the foetus, but this is probably because the titre gives no indication either of the quantity of antibody crossing the placenta, or of the quantity taken up by the foetal cells.

Summary

Families containing babies with haemolytic disease of the newborn have been classified into two main groups depending on the gravity of the disease in the first affected baby. If this first affected baby has a mild form of the disease, i.e. is not hydropic or stillborn, then in 83% of cases the next affected will also be a mild case. If this first affected baby is hydropic

or stillborn, then in 80% of cases the next affected will also be hydropic or stillborn, if delivered at term.

Women whose first affected baby is hydropic or stillborn have three times as many subsequent pregnancies as do those whose first affected is a mild case; the women who are least likely to have a viable infant endeavour most to obtain one. If such women are allowed to go into labour spontaneously the baby will usually be stillborn or hydropic; it is suggested that, unless the husband is heterozygous, in these cases the premature induction of labour is indicated.

By contrast, women whose first affected baby is a mild case need not necessarily be discouraged from having another infant because affected children born subsequently are usually mild cases also.

The severity of the disease in the foetus appears to be greatest in the offspring of women who have had the fewest unaffected children or who have had transfusions of non-homologous Rh blood, i.e. the disease is most severe in the offspring of women who are most easily sensitized or who have had the most powerful antigenic stimulus.

We are very grateful to Dr. W. Weiner for his help in this study, and to Dr. Frances Braid, Dr. V. Mary Crosse, Mr. H. B. Watson and the many obstetricians and paediatricians who have given us access to their cases.

Part of the expenses of this investigation were defrayed from a grant from Messrs. Cow and Gate Ltd.

REFERENCES

- Allen, F. H., Diamond, L. K. and Vaughan, V. C. (1950). *Pediatrics*, **6**, 441.
 Allott, E. N. (1951). In *Modern Trends in Paediatrics*. Ed. Sir Leonard Parsons. London.
 Arnold, B. J., Walsh, R. J. and Herzger, R. (1951). *Med. J. Aust.*, **1**, 301.
 Bevis, D. C. A. (1952). *Lancet*, **1**, 395.
 Davies, B. S., Gerrard, J., Hatchuel, W. L. F. and Howarth, B. E. (1953). *Birm. med. Rev.*, **18**, 77.
 Diamond, L. K. (1950). In *Mitchell-Nelson Textbook of Pediatrics*. Ed. W. E. Nelson. Philadelphia and London.
 —, Allen, F. H., Vann, D. D. and Powers, J. R. (1952). *Pediatrics*, **10**, 337.
 Ellis, R. W. B. (1951). *Disease in Infancy and Childhood*. Edinburgh.
 Levine, P. (1943). *J. Hered.*, **34**, 71.
 Race, R. (1952). In *The Rh Blood Groups and their Clinical Effects*. M.R.C. Memorandum No. 27. P. L. Mollison, A. E. Mourant and R. R. Race.
 Salomonsen, L. (1952). In *Fanconi and Wallgren's Textbook of Paediatrics*. Ed. W. R. F. Collis, London.
 Sheldon, W. (1951). *Diseases of Infancy and Childhood*, 6th ed. London.
 Watson, H. B. (1953). Personal Communication.
 Whitby, L. and Newns, G. H. (1953). In *Garrod, Batten and Thursfield's Diseases of Children*, 5th ed., Vol. II. Ed. A. Moncrieff and P. Evans, London.