THE Rh FACTOR AND ERYTHROBLASTOSIS FOETALIS

AN INVESTIGATION OF 50 FAMILIES

BY

R. R. RACE,* M.R.C.S., L.R.C.P. G. L. TAYLOR,* M.D., Ph.D., M.R.C.P. D. F. CAPPELL, M.D.

AND

MARJORY N. McFARLANE, M.B., Ch.B.

(From the Galton Laboratory Serum Unit, Department of Pathology, Cambridge, and the Pathology Department, University of St. Andrews and Royal Infirmary, Dundee)

Recent American work has shown that iso-immunization plays an important part in the aetiology of erythroblastosis foetalis, a familial disease of the newborn, which Parsons, with justification, thinks would be better called "haemolytic disease of the newborn."

The part played by iso-immunization in this condition has been described at length by Levine, Burnham, Katzin, and Vogel (1941) and by Boorman, Dodd, and Mollison (1942). In their view, erythroblastosis foetalis results from iso-immunization of the mother to a red-blood-cell antigen present in the foetus, inherited from the father but absent in the mother herself, and the subsequent passage of the mother's immune agglutinins through the placenta to act on the susceptible blood of the foetus. In most cases described by the above authors iso-immunization to the Rh blood-group factor appeared to be responsible, as more than 90% of the mothers were Rh-negative and an antibody to the Rh factor was found in the serum of many of them. The Rh factor is inherited as a dominant character. Whenever it was possible to examine the blood of an erythroblastotic baby of an Rh-negative mother it proved to be Rh-positive. The finding that more than 90% of mothers of erythroblastotic children are Rh-negative when only 15% of the normal population are Rh-negative is in itself so overwhelmingly significant statistically that a connexion between the Rh groups and this disease can hardly be doubted, even apart from the evidence provided by the detection of the antibody in many of the cases.

It can be shown that in one pregnancy in ten the mother is Rh-negative and the baby Rh-positive, and that in one pregnancy in five the mother has an agglutinin for an antigen of the A-B-O system of groups present in her foetus. Haemolytic disease of the newborn is, however, much rarer than would be expected if iso-immunization and placental transmission of harmful agglutinins from mother to foetus occurred in every instance in which the possibility exists. It is obvious, therefore, that there is yet much to be learned about the way in which iso-immunization operates in such families. The subject is undoubtedly of importance in obstetrics and in paediatrics, and while at the moment it is not clear what facts may prove of importance in extending our knowledge, it is essential that no opportunity of making serological investigations should be lost.

The object of the present paper is to put on record our findings in the examination of 50 families in which erythroblastosis foetalis has been diagnosed, and a list of their pedigrees forms the main part of this communication. The cases have been sent to us by practitioners and pathologists from many parts of the United Kingdom and from Northern Ireland, and in those reported it seems reasonably certain that the diagnosis of erythroblastosis foetalis was correct. The material is far from complete, for the great difficulties always present in the

pursuit and investigation of human families are in wartime enormously increased. For instance, men and women are away from home in the Forces; travelling is difficult; and, with doctors so fully occupied, personal visiting is practically impossible. Nevertheless, much information has been gathered together, and some of it may well prove of value to future workers. The technique used for detecting the Rh factor and its antibody has been described by Taylor (1943).

Results

Of the 50 mothers 6 were Rh-positive and 44 were Rh-negative; while in the sera of 38 of these Rh-negative women anti-Rh agglutinins were found. If Rh were not concerned in the causation of erythroblastosis foetalis only 7 or 8 of these 50 women would be expected to be Rh-negative; that 44 were Rh-negative and that Rh antibody was present in the serum of the great majority confirms the connexion between this recently discovered blood-group factor and the disease. In spite of the absence of demonstrable anti-Rh agglutinins in the remaining six Rh-negative cases it is highly probable that iso-immunization of the mother to the Rh factor played a part; the absence of anti-Rh may in some of them have been due to the length of time since delivery, which on the average was four years as against less than a year for the 38 cases in which antibody was found. In none of the six was there any certain evidence of other blood-group factors being involved. That as many as six of the twelve mothers in whose serum anti-Rh was not found were Rh-negative strongly suggests that Rh was concerned.

While Rh is the blood-group factor most commonly involved in the causation of erythroblastosis foetalis, it appears certain that other red-cell antigens may behave in a similar way. As mentioned above, in one pregnancy in five the mother's serum contains an iso-agglutinin for an antigen of the A-B-O system of groups present in her foetus. (This will always be so where the foetus is of group AB, save in about one case in six in which the mother will also be of group AB.) In such a heterospecific pregnancy the mother's natural iso-agglutinins might perhaps cause the destruction of her child's red cells. Even when the mother is Rh-negative iso-immunization to some antigen other than Rh might be concerned in the causation of erythroblastosis. For example, in one case recently studied (but not included in the 50 cases of this series) the mother was of group A₂B Rh-negative and her husband and baby were both A₁ Rh-positive; anti-Rh agglutinins were present in good amount in her serum, but in addition a very strong alpha₁ agglutinin (with A₁ Rh-negative cells titre at room temp. 128-256, at 37° C. 32) was also present. It would appear that this woman had become iso-immunized against both A₁ and Rh contained in the cells of the foetus, for the strength of the alpha₁ was greater than we have found in grouping more than 100,000 persons (see Taylor, Race, Prior, and Ikin, 1942). It seems probable that the erythroblastosis from which her baby suffered may have been due to placental transmission

* Working on behalf of the Medical Research Council.

Family No.	Mother's Age in 1942	Mother's Group		Father's Group		Mother's Serum		Pregnancies					Notes
		Rh	ABO	Rh	ABO	Anti-Rh	Taken after Delivery	1	2	3	4	5	
1	25	—	A ₁	+	B	Found	4 mths.	M, 1940, A.W.	M, 1942, I.G.N., d. 2 days				
2	32	+	O	—	A	Not found	3 mths. before delivery of last child	M, 1940, E.F., d.	M, 1942, A.W.				1st child showed hydrops and jaundice
3	22	—	O			Found	7 mths.	F, 1940, A.W., Gp. O Rh+	F, 1941, jaundice, d. 10 days				p.m. diagnosis: "leuco-erythroblastic anaemia"
4	34	—	A ₂			Found	14 mths.	M, 1926, A.W.	M, 1927, d. 1 year lung abscess	F, 1930, A.W.	M, 1932, A.W.	F, 1933, d. 3 mths. pneumonia	7th child died of umbilical haemorrhage 1 mth.; 8th child jaundiced after birth
								6 M, 1934, A.W.	7 M, d. 1 mth.	8 M, 1938, A.W.	9 M, 1939, A.W.	10 F, 1941, E.F., d. 6 days	
5	32	—	O	+	A ₁	Found	2 years	F, 1935, A.W.	Misc., 1939	F, 1940, I.G.N. Surv.			1940 child mentally and physically backward
6	33	—	A ₁			Found	20 mths.	F, 1935, A.W., Gp. A ₁ Rh+	M, 1939, I.G.N., d. 2 days	Misc., 1941, 6½ mths.			Mother Wassermann reaction + in 1941. 1943: Still under treatment at V.D. clinic
7	36	—	A ₂			Found	Few days	F, 1931, A.W.	M, 1933, A.W.	SB, male, 1937, Full time	M, 1942, d. 5 days, jaundice		1937: SB was anencephalic and had foetal ascites 1942 child—hydramnios
8	45	—	A ₁	+	O	Found	10 days and 7 mths.	M, 1929, A.W., Gp. A ₂ Rh+	M, 1931, A.W., Gp. A ₁ Rh+	F, 1940, A.W., Gp. A ₁ Rh+	F, 1942, E.F. Surv. Gp. A Rh+		4th child jaundiced from 2nd to 5th day
9	32	—	A ₁			Found	3 years	F, 1929, A.W., Gp. O Rh+	M, 1931, A.W., Gp. O Rh+	M, 1933, A.W., Gp. A ₁ Rh+	Misc., 1935, 9 wks.	M, 1936, d. 10 wks. imperforate anus	SB child—7 mths. premature—hydramnios, E.F. confirmed p.m. 7th child a few weeks premature
								6 SB, female, 1937, H.F.	7 M, 1939, d. at birth				
10	32	—	B	+	A ₁ B	Found	During last pregnancy	F, 1936, A.W., Gp. B Rh+	M, 1939, I.G.N., d. 4 days	F, 1943, I.G.N., d. 4 days Gp. A ₁ Rh+			Antibody first found when 4 mths. pregnant with last child
11	42	—	A ₁	+	A ₁	Found	8 years	SB, 1919, premature	M, 1921, A.W.	F, 1922, A.W.	SB, 1923, premature	SB, 1926, premature	Mother sterilized in 1935 p.m. exam. of 7th and 8th babies confirmed diagnosis 8th child had other congenital abnormalities
								6 SB, 1928, premature	7 M, 1932, I.G.N., d. 6 days	8 M, 1934, I.G.N., d. 2 days			
12	22	—	O	+	O	Found	10 days	F, 1939, A.W.	F, 1942, I.G.N. Surv. Gp. O Rh+				Last child had umbilical haemorrhage
13	33	—	A ₁			Found	8 days	SB	U d. 4 days jaundice	F, 1942, I.G.N. Surv.			Stillbirth macerated
14	24	—	O			Found	1 day	U, 1937, d. 5 days	U, 1938, A.W.	U, 1940, A.W.	F, 1942, E.F., d. 3 wks. Gp. O Rh+		3rd child was jaundiced on 3rd day
15	32	—	A ₁	+	A ₁	Found	9 mths.	M, 1937, A.W., Gp. A ₁ Rh+	M, 1938, I.G.N., d. 4 wks.	M, 1940, I.G.N., d. 10 wks.	M, 1942, A.W., Gp. A ₁ Rh+		p.m. on 2nd and 3rd children: "marasmus, icterus, liver firm"
16	36	+	A ₂			Not found	2 days	F, 1934, A.W.	M, 1935, A.W.	SB, 1942, H.F.			Stillbirth, male; hydramnios
17	37	—	O	+	B	Found	During last pregnancy and 8 days after last confinement	M, 1934, A.W., Gp. B Rh+	H.F.		F, 1936, Gp. O Rh+	M, 1938, I.G.N., d.	2nd and 3rd children twins; hydramnios
								6 M, 1942 E.F. Surv. Gp. B Rh+	Misc., 1935, 3-4 mths.	Misc., 1935, 3-4 mths.			
18	25	—	O	+	O	Found	2 days	M, 1937, A.W., Gp. O Rh+	M, 1938, I.G.N. Surv. Gp. O Rh+	F, 1942, H.F., d. few days			
19	37	—	A	+	O	Found	1st day and 7th day	M, 1933, Gp. O Rh+	M, 1935, Gp. A ₁ Rh+	F, 1942, E.F., d. minutes			
20	34	—	B			Found	8 mths.	F, 1929, A.W.	F, 1931, A.W.	F, 1933, A.W.	M, 1940, A.W.	F, 1941, E.F. Surv.	Last child—4 wks. premature. Jaundiced, splenectomy at 1 mth.
21	35	—	O	+	A ₁	Found	6 weeks	F, 1936, A.W., Gp. A ₁ Rh+	M, 1940, A.W., Gp. O Rh+	M, 1942, E.F., d. 3 days			Last child jaundiced after 5 or 6 hours. 3 wks. premature
22	42	—	A ₁ B			Found	4 years	M, 1921, A.W.	M, 1921, d. 3½ yrs.	F, 1923, A.W.	M, 1925, d. 4 wks., jaundiced	F, 1926, A.W., Gp. B Rh+	4th child diagnosis: "congenital obliteration of the bile ducts" 7th and 8th children twins 9th child p.m. I.G.N. confirmed
								6 M, 1928, A. TB. Gp. B Rh+	7 F, 1929, A.W., Gp. B Rh+	8 F, 1929, d. 9 mths. "convulsions"	9 M, 1935, I.G.N., d.	10 F, 1938, I.G.N., d.	

For key to abbreviations, etc., see end of table.

Family No.	Mother's Age in 1942	Mother's Group		Father's Group		Mother's Serum		Pregnancies					Notes
		Rh	ABO	Rh	ABO	Anti-Rh	Taken after Delivery	1	2	3	4	5	
23		-	O	+	O	Found	3 years	F, 1931, A.W. 6 F, 1939, E.F. Surv. Gp. O Rh +	F, 1932, A.W.	F, 1935, A.W.	F, 1935, A.W.	F, 1937, A.W.	Last child deeply jaundiced at birth
24		-	A ₂	+	O	Not found	9 mths.	U, 1938, A.W.	U, 1941, E.F. Surv. Gp. O Rh +				Last child jaundiced at birth
25	18	+	O			Not found	1st day	SB, 1942, E.F.					8 mths. foetus; p.m.: "liver showed advanced erythroblastosis" Very oedematous
26	30	+	O	-	O	Not found	Now pregnant	F, 1930, A.W. Gp. O Rh +	M, 1935, A.W. Gp. O Rh +	F, 1939, A.W. Gp. O Rh +	M, 1940, I.G.N. Surv. Gp. O Rh +		4th child is an idiot and is partially paralysed
27	32	-	B			Found	14 mths.	F, 1934, A.W.	M, 1936, A.W.	F, 1939, A.W.	F, 1941, I.G.N. Surv. Gp. O Rh +		Last child mentally backward. Born jaundiced
28	29	-	AB			Found	Less than 1 year	U, 1937	SB, male, 1938, 7½ mths.	SB, male, 1940, 8 mths.	SB, female, 1941, 7½ mths.	SB, 1942, E.F.	p.m. report (on last child) suggests E.F.
29	26	+	AB			Not found	6 mths.	U, 1942, E.F., d. 12 wks.					p.m.: "typical of E.F." First and only child
30	34	-	A ₁ B	2nd husband +	A ₁	Found	5 weeks	By 1st husband F, 1930, A.W. Gp. B Rh +	By 2nd husband F, 1941, I.G.N., d. 3 days	M, 1942, I.G.N. Surv. Gp. A ₁ Rh +			
31		-	A			Not found	8 years	M, 1920, A.W. 6 M, 1932, A.W.	M, 1922, A.W. 7 M, 1933, A.W.	M, 1925, A.W. 8 U, 1934, I.G.N., d. 5 wks.	F, 1929, A.W. Gp. A ₁ Rh +	M, 1931, A.W. Gp. A ₁ Rh +	8th child jaundiced on 2nd day
32	30	-	O	+	A ₁	Found	22 mths.	M, 1934, A.W. Gp. A ₁ Rh +	M, 1936, I.G.N. Surv. Gp. O Rh +	M, 1936, I.G.N., d. 4 days	M, 1938, I.G.N., d.	F, 1941, I.G.N., d.	2nd and 3rd children twins
33		-	O			Not found	11 years	M, 1922, A.W.	F, 1926, A.W.	U, 1931, I.G.N.			Last child born with jaundice and enlarged liver and spleen
34	35	-	A ₁	+	O	Found	2 wks., still present 1 year later	M, 1939, A.W. Gp. A ₁ Rh +	F, 1942, I.G.N., d. 8 days. Gp. A				
35	32	-	O	+	O	Found	3 days	M, 1931, A.W.	M, 1934, A.W.	F, 1938, I.G.N., d. 9th day	M, 1942, I.G.N. Surv. Gp. O Rh +		1938 child's jaundice appeared on 3rd day
36	24	-	A ₂	+	A ₂	Found	1 year	F, 1938, A.W. Gp. O Rh +	F, 1941, E.F., d. 18 hours				Last child jaundiced at birth
37	34	-	A ₁	+	O	Not found	3 years	Misc., 1932, 3 mths.	F, 1935, d. 3 days jaundiced	Misc., 1939, 4 mths.			2nd child premature 7 mths.
38	35	-	A ₁	+	A ₁	Found	3 mths.	F, 1929, A.W. Gp. O Rh + 6 SB, 1937, F, premature	F, 1930, I.G.N., d. 3 days 7 M, 1938, I.G.N., d. 2 days	M, 1931, I.G.N., d. 3 days 8 M, 1940, I.G.N., d. few hours	M, 1934, I.G.N., d. 3 days 9 F, 1942, I.G.N. Surv.	M, 1936, I.G.N., d. 3 days	
39	32	-	A ₁	+	O	Found	During last pregnancy	M, 1931, A.W. 6 M, 1940, I.G.N., d. 4 days	F, 1932, A.W. 7 M, 1941, E.F., d.	F, 1934, A.W.	M, 1935, A.W.	M, 1938, A.W.	6th child's jaundice appeared on 3rd day. 7th child's on 2nd day p.m. confirmation of 7th child's diagnosis
40	27	-	B	+	O	Found	1 week	U, 1940, A.W.	M, 1942, H.F., d. 1 hr. Gp. O Rh +				Dead child was jaundiced p.m. confirmation of diagnosis
41	39	-	A ₁		B	Not found	1 mth.	M, 1927, A.W.	F, 1932, A.W.	M, 1942, E.F. Surv.			
42	40	-	O			Found	Few days	U, A.W. 6 U, 1942, H.F., d. few days	U, A.W.	U, A.W.	U, A.W.	U, 1941, I.G.N., d. 8 days	6th child delivered by hysterotomy for placenta praevia
43	34	-	A ₁	+	O	Found	2 weeks	SB, 1940	SB, female, 1942, H.F.				Diagnosis confirmed p.m.
44	22	-	O	+	A ₁	Not found	3rd day and 10th day	M, 1942, I.G.N., d. 3 days Gp. O Rh +					1st (and only) child premature 7 mths. Born jaundiced, p.m. confirmation of diagnosis

For key to abbreviations, etc., see end of table.

Family No.	Mother's Age in 1942	Mother's Group		Father's Group		Mother's Serum		Pregnancies					Notes
		Rh	ABO	Rh	ABO	Anti-Rh	Taken after Delivery	1	2	3	4	5	
45	38	+	O			Not found	3 weeks	SB, 1942, I.G.N.					Full term. First (only) child
46		-	B	+	O	Found	14 mths.	Misc., 3 mths.	M, 1933, A.W. Gp. B Rh+	Misc., 3 mths.	M, 1936, A.W. Gp. B Rh+	F, 1937, A.W. Gp. O Rh+	The last miscarriage suffered from hydrops
								6 F, 1939, I.G.N., d. 36 hours	7 SB, female, 1940, H.F. 7 mths.	8 Misc., H.F. 5 mths.			
47	32	-	A ₁			Found	1 week	M, 1934, A.W.	F, 1935, d. 9 days, melaena	F, 1936, A.W.	F, 1937, A.W.	F, 1938, A.W.	p.m. confirmation of diagnosis of 8th child
								6 SB, female	F, 1941, d. 6 weeks microcephaly	8 F, 1942, I.G.N., d. few hours			
48	31	-	O			Found	19 mths.	M, 1935, A.W. Gp. O Rh+	M, 1937, d. 4 mths.	Misc., 1940,	F, 1941, d. 1 day		2nd child died of "diseased liver"
49	34	-	A ₁			Found	1 mth.	U	F, 1942, I.G.N. Surv. Gp. A ₁ Rh+				No information concerning miscarriages, if any. 2nd child jaundiced on second day. Oedema of legs and abdomen
50	42	-	A ₁	+	O	Found	2 weeks	F, 1932, A.W. Gp. O Rh+	U, 1936, d. 1 hour, "cancer"	Misc., 1941, 4 mths.	F, 1942, I.G.N. Surv. Gp. A ₁ Rh+		Mother's Wassermann reaction negative. 4th child's jaundice persisted for 1 mth.

F=Affected female. M=Affected male. U=Affected, sex unknown. SB=Affected stillbirth.

F=Unaffected female. M=Unaffected male. U=Unaffected, sex unknown. SB=Stillbirth, not diagnosed as erythroblastic.

A.W.=Alive and well. d.=died. Gp.=Blood group. Misc.=Miscarriage (termination of pregnancy before 28th week). p.m.=Post-mortem examination

Surv.=Survived. H.F.=Hydrops foetalis. I.G.N.=Icterus gravis neonatorum. E.F.=Erythroblastosis foetalis.

The last three represent diagnosis as reported to us.

49 of the 50 families in this table were mentioned by Taylor (1943).

of both these agglutinins. When the mother is Rh-positive it seems certain, if iso-immunization is responsible, that another antigen must be involved. In 6 of the families in the above series the mother was Rh-positive, but in only one of the 6 (No. 26) were we able to examine the blood of the affected child. Both mother and child were O Rh-positive, the father O Rh-negative; obviously in this case the A-B-O groups could not be involved. We were able to examine the blood of the husbands of only two of these six Rh-positive mothers; both these men were Rh-negative. Since then, however, we have examined two further cases of Rh-positive mothers with affected children; in one the husband was Rh-negative, in the other he was Rh-positive. In this last case the serum of the mother (group O Rh-positive) contained a very powerful antibody more active at 37° C. than at room temperature. This serum gave clear-cut positive reactions with the red cells of 80% of a large number of unselected group O persons, including her erythroblastic child (group O Rh-positive). When tested against group O Rh-negative bloods it was found to agglutinate strongly a series of 50 consecutive samples. After removal of the anti-A and anti-B iso-antibodies the serum still agglutinated the husband's cells (group A₁ Rh-positive). This antibody is not specific for any of the blood-cell antigens A, B, O, M, N, P, Rh, but it is suspected that it is similar to the irregular agglutinin found by Levine, Javert, and Katzin (see Levine, 1941) in the blood of an Rh-positive mother with Rh-negative husband and an erythroblastic child, and named by them anti-Hr. According to Wiener (1942) this irregular agglutinin acts on Rh-negative cells and certain Rh-positive cells, which he designates Rh₂ on the analogy of the subdivisions of the A group. The work of Davidsohn and Toharsky (1942) indicates that the subdivision of the Rh factor is much more complex than this, and our experience bears this out. We are of the opinion that our finding of three out of four husbands of Rh-positive mothers with affected children to be Rh-negative is significant, and similar cases have been recorded by Javert (1942a, 1942b). These latter families are not among the 50 reported in this paper; it is hoped to publish further details about them when more information is available.

It is possible that mistakes in diagnosis may contribute to the small group of families with Rh-positive mothers. For example, this series of families originally included one with a child at first thought to be erythroblastic but which was later shown to have acholuric jaundice. Such a family, really not erythroblastic at all, if mistakenly included in a series

of erythroblastic families would in six cases out of seven fall into the group where the mother is Rh-positive, for there is no reason why mothers of, say, acholuric babies should not have the normal distribution of Rh groups.

There are other points arising from our findings that have interested us very much. In particular, we have failed to find a single Rh-negative child among the offspring of these 44 Rh-negative mothers; we have tested 33 healthy and 16 affected children. The absence of Rh-negative children from the healthy group is highly significant, and may be provisionally explained by two circumstances, both favourable to the predominance, among families showing the condition, of those of which the fathers are homozygous. There is reason to think (1) that all Rh-positive children of Rh-negative mothers are not equally liable to the disease—

In most families two or three positive children seem to be necessary before an affected child is produced, and where the father is homozygous (RhRh) and all his children are positive, these conditions are more likely to be met than when he is heterozygous (Rhrh) and there is an equal chance that each conception may produce Rh-positive or Rh-negative children;

(2) that ascertainment is more frequent when the affected child has an affected sibling than when it is the only affected child in the family.

It can readily be shown that, in the absence of unforeseen disturbances, approximately three out of seven Rh-positive males must be homozygous, while four must be heterozygous. Since half the children of the heterozygotes by Rh-negative wives must be Rh-negative, the proportion of these is two-sevenths of all the children of marriages between Rh-positive men and Rh-negative women. If, therefore, it was sufficient to determine haemolytic disease for a child of an Rh-negative mother to be Rh-positive, and if all such cases had the same probability of ascertainment, we should expect one-fifth of their sibs, taking haemolytic and normal together, to be Rh-negative.

Of 5 Rh-positive children the sibs of 3 (those of homozygous fathers) would all be positive; of the other 2 positive children (of heterozygous fathers) half the sibs would be positive—i.e., of all the sibs of Rh-positive children four-fifths would be positive and one-fifth negative.

This expectation is clearly contradicted by our finding in this series—none negative out of 33 normal.

If, on the other hand, to take a second simple hypothesis for comparison with the facts, we suppose that a necessary

and sufficient condition for the appearance of the disease is that both the subject and the next prior sib must be Rh-positive, all single-child families would be excluded from the record, while for all sizes of family greater than one the representation of families having heterozygous fathers would again be halved, so that three families out of four would be the children of homozygotes. Of the children, excluding both the propositus and the child next preceding it, only one in eight would be expected to be Rh-negative. In our material this exclusion left 26 children grouped for Rh; of these only 3.25 would be expected to be Rh-negative, which is not incompatible with the absence of observed cases.

The scarcity of Rh-negative children will have to be taken into consideration in estimating the chances of getting an Rh-negative (that is, an unaffected) child in such families. If it has been possible to show, by finding an Rh-negative child, that the father is heterozygous, the chance of the next child being normal is one in two. In the absence of this indication prognosis is entirely unfavourable.

That an Rh-negative child may occur in an affected family has been shown by our finding very recently a family in which the first child was Rh-negative, the second Rh-positive, while a third died from jaundice. The blood of this child was not examined, but the mother was Rh-negative and her serum contained an anti-Rh agglutinin. In our present series, with one exception, no mother who has once produced an erythroblastotic baby has ever had a normal surviving child. The exceptional child is the fourth of Family 15, and while we have been unable to obtain any evidence of his having been affected, he is Rh-positive, though only with certain sera. It is perhaps significant that his cells on several occasions failed to react with his mother's serum (on one occasion there was a suggestion of a weak reaction), whereas the cells of the first-born reacted strongly.

Of the first children borne by the 44 Rh-negative mothers 38 were unaffected, 5 were stillbirths or miscarriages, and 1 (No. 44) is known to have suffered from the disease. Although anti-Rh was not found in the mother's serum in this last case, it is likely that this factor was responsible, for the baby was O Rh-positive; so it does not seem possible that the A-B-O system of groups could have been involved. From the second birth onwards there was a steadily increasing ratio of affected to normal children. Four of the six Rh-positive mothers, on the other hand, had first children with the disease; two of these three were affected stillbirths. The earlier onset in this group might be due, if the A-B-O system of groups were responsible, to the iso-agglutinins being already present in the mother's serum, though in only one of the four cases is the father's group known to be such that a heterospecific pregnancy could occur.

In our series about a quarter of the children diagnosed as affected survived; three-quarters were born dead or died mostly within a week of birth. Although miscarriages and stillbirths not diagnosed as affected are not represented in these proportions it is probable that the same causes were operative in a substantial proportion; on the other hand, mild cases which recover may not find their way into such a series. Affected children were approximately evenly distributed between the two sexes.

We are grateful to the following pathologists and practitioners for sending us samples of blood and case details: E. F. Aubert, T. H. Boon, W. Broughton-Alcock, F. J. Burke, F. E. Camps, A. E. Chisholm, J. B. Cochrane, J. Craig, J. J. Dubash, Caroline A. Elliott, Margaret Fairlie, J. S. Faulds, A. Hanton, J. S. Hesketh, D. V. Hubble, P. H. Kendall, N. Lissimore, S. Lucas, A. J. McCall, S. G. M. Mackay, H. Mallinson, L. C. Martin, M. E. Matthews, S. F. Moores, J. Murray, G. R. Osborne, W. S. Stanbury, R. Williams, and C. H. Wrigley. We also wish to thank Prof. R. A. Fisher for help with the paragraphs dealing with the absence of Rh-negative children in our material.

REFERENCES

- Boorman, K. E., Dodd, B. E., and Mollison, P. L. (1942). *British Medical Journal*, **2**, 535.
 Davidson, I., and Toharsky, B. (1942). *Amer. J. clin. Path.*, **12**, 434.
 Javert, C. T. (1942a). *Surg. Gynec. Obstet.*, **74**, 1.
 (1942b). *Amer. J. Obstet. Gynec.*, **43**, 921.
 Levine, P. (1941). In *Year-book of Pathology and Immunology*, p. 509, Chicago.
 — Burnham, L., Katzin, E. M., and Vogel, P. (1941). *Amer. J. Obstet. Gynec.*, **42**, 925.
 Taylor, G. L. (1943). *Proc. roy. Soc. Med.*, **36**, 225.
 Race, R. R., Prior, A. M., and Ikin, E. W. (1942). *J. Path. Bact.*, **54**, 514.
 Wiener, A. S. (1942). *Amer. J. clin. Path.*, **12**, 302.

HAEMOLYTIC DISEASE OF THE NEWBORN (ERYTHROBLASTOSIS FOETALIS)

ITS TREATMENT WITH RHESUS-NEGATIVE BLOOD*

BY

JANET D. GIMSON, M.B., B.S.

Resident Assistant Physician to the Hospital for Sick Children,
Great Ormond Street

A series of 19 consecutive cases of haemolytic disease of the newborn, collected during the eleven months from March, 1942, to Feb., 1943, at the Hospital for Sick Children, Great Ormond Street, is here surveyed. Following on the work of Levine *et al.* (1941a, 1941b) on the iso-immunization theory of causation of erythroblastosis foetalis, it was desired to treat these infants by transfusion with rhesus-negative blood, free of agglutinins, and thus test out the recommendation that rhesus-negative blood would produce better results than rhesus-positive blood. The blood of the infants and mothers was tested with this theory in view.

Briefly, the iso-immunization theory may be stated thus: A man whose blood contains the Rh factor mates with a woman whose blood does not contain the Rh factor. If her foetus is Rh-positive she may produce anti-Rh agglutinins as a result of immunization with the foetal blood. The antibodies pass through the placenta, and in suitable concentration cause haemolysis of the foetal red cells. Several workers—Wiener in 1942, and Boorman, Dodd, and Mollison (1942)—have shown that a little less than 15% of a random sample of the population have blood which does not contain the rhesus factor—namely, is Rh-negative. In 1941 Landsteiner and Wiener showed that the Rh factor is inherited as a dominant Mendelian character. The Rh-positive child of an Rh-negative mother inherits the factor from the father, and if the mother responds by making anti-Rh the foetus is likely to be affected by haemolytic disease. If in such a family the father is heterozygous (Rhrh) each child will have an even chance of being Rh-negative and so of escaping the disease, but if he is homozygous (RhRh) every child will be Rh-positive and likely to be affected. The difference in clinical forms is probably due to varying degree and duration of iso-immunization during the course of pregnancy. Although immunization to the Rh factor appears to be responsible for the great majority of cases of haemolytic disease (Levine *et al.*, 1941a, 1941b; Boorman *et al.*, 1942) other group factors are evidently responsible in cases where the mother is found to be Rh-positive.

The consequent anaemia in the foetus calls forth a great effort of response from all erythropoietic tissue. This has often been shown post mortem by previous workers, and is usually demonstrable in varying degree in the blood during life. Parsons, Hawksley, and Gittins in 1933, and Hawksley and Lightwood in 1934, laid stress on the fact that there was more evidence for there being a primary haemolytic cause for erythroblastosis than for a primary disturbance of blood formation. The possibility of a hereditary transmitted factor had not then been adequately investigated.

Present Series of Cases

This series of 19 cases (see Table) is necessarily a selected group of this disease. The selection is automatic and is therefore typical of those cases coming to any children's hospital which is not directly attached to a maternity hospital; for macerated foetuses and stillborn infants are not seen, and it is rare for cases of hydrops foetalis or icterus gravis neonatorum, which are fatal within 24 hours of birth, to be sent in before death. Seventeen were primarily cases of icterus, with or without anaemia; two were anaemic only and showed no jaundice. Two had transient oedema of the eyelids; one had ascites in addition to jaundice and pallor. One case appeared mentally defective. The age when admitted to hospital varied between 3 days and 6 weeks; 4 came within the first week of life; 13 within the first fortnight.

* Substance of a communication to the British Paediatric Association, May, 1943.