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HAEMOLYTIC DISEASE OF THE NEWBORN AS A FAMILY PROBLEM

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In the management of haemolytic disease of the newborn we are continually faced with the need to advise parents about the probable pattern which this disease will impose on their family life. In the absence of previous transfusion we can assure the primigravida that there is virtually no risk. On the other hand, once antibodies have developed every subsequent rhesus-positive foetus will be affected to some degree. The prediction of the probable severity in any affected baby would be of great help to parents and doctor alike, and should be possible if the disease in successive pregnancies follows one or a limited number of consistent patterns.

The purpose of this paper is to ask, in the light of the extensive experience of this disease which now exists, whether such patterns can be traced in affected families and to what extent they form a reliable basis for judgment in the individual case.

We must admit that widely divergent views have already been stated on this question. The extremes are well expressed by Potter (1953) and Vaughan (1953) respectively: "It is my belief, based on our own experience, that almost all immunized women can look forward to stillbirths if they have enough pregnancies," and, "If a woman tries often enough she is almost bound to bear a living baby." While many authorities recognize that mild disease may follow a severely affected baby (Chown, 1948; Zuelzer *et al.*, 1948; Allot, 1951), the view that each successive foetus is more severely affected than the last has found its way into most textbooks dealing with the subject (Diamond, 1950; Ellis, 1951; Whitby and Newns, 1953; Sheldon, 1955), and, indeed, it can be shown statistically that there is a general trend towards a more severe form of the disease in successive pregnancies (Potter, 1948, 1953; Zuelzer *et al.*, 1948). The validity of its application to the individual family—for example, to help in selecting cases for exchange transfusion (Mollison and Cutbush, 1954)—is questionable. Davies and her co-workers (1953) provide some explanation for these differing views by suggesting that there are two types of family—the one starting with "mild" disease (by which they mean liveborn affected babies) and followed by "mild" disease in 83% of cases, the other starting with the "severe" (stillborn) variety and followed by a similar outcome in 80% of instances.

Though there is a measure of truth in these differing views, our experience suggests that certain sequences in the family history are constant enough to serve as a reliable guide to the risks in affected families.

Material and Methods

This account is based on observations of 1,336 pregnancies in 1,033 families in Northumberland and Durham during an eight-year period, from mid-1947 to mid-1955. During the last four years five cases have been recognized for every 1,000 births, but, previous to this, detection was 4 per 1,000, mainly because sub-clinical cases were overlooked in the absence of full serological studies. This would result in the general pattern being shifted to the severe varieties, but it was nevertheless thought that comparisons would be valid when based on individual family histories.

In the early years we found that the recorded histories were often inadequate or incorrect, and in 1951 one or other of us personally interviewed all but 13 of the mothers immunized up to that time.

Since 1951 practically all cases have been delivered in the Newcastle group of hospitals, and members of the obstetric or paediatric staff have made a special point of taking a detailed history. Nevertheless, in any case where the story suggested previous haemolytic disease we have amplified it by contact with the home doctor, the hospital concerned, or the patient herself. Similarly, whenever there has been a history of previous transfusion we have taken all reasonable steps to discover the amount and Rh group of the blood used. Finally, in the families where we have observed haemolytic disease in a second pregnancy we have checked that this was indeed the second pregnancy.

Criteria for Diagnosis.—We have preferred serological proof to clinical evidence, and obtained such in 86% of cases during 1947–51 and in 95% of cases since that time. In general we have accepted as haemolytic disease:

1. A baby with a positive Coombs reaction during the neonatal period.
2. An Rh-positive baby of an immunized Rh-negative mother.
3. Any baby of an immunized Rh-negative woman and a homozygous Rh-positive man when the baby (often still-born) was not tested.

4. A clinical or pathological diagnostic picture but where serological proof was incomplete. Under this heading we have accepted: (a) Definite jaundice in the first 24 hours of life for which no other cause could be found. (b) Severe anaemia in the neonatal period, relieved by blood transfusion and leaving no clinical or haematological abnormality. (c) Kernicterus in a mature baby or in a premature baby with other features suggestive of haemolytic disease. (d) Hydrops foetalis where no other cause could be found.

Criteria of Severity.—With present methods of prediction and early exchange transfusion in selected cases, we find the older clinical classifications no longer of much value and have substituted the accompanying new classification.

Classification of Severity of Haemolytic Disease

Liveborn:

Not requiring treatment (Mild, 40%)

Requiring treatment (60%)

Moderate:

1. Cord Hb 12–14.8 g. per 100 ml.
2. Cord bilirubin >2.7 mg. per 100 ml.
3. Anaemia with or without mild jaundice

Severe:

1. Cord Hb 9–12 g. per 100 ml.
2. Cord bilirubin >4 mg. per 100 ml.
3. Early severe jaundice
4. Kernicterus

Very severe:

1. Cord Hb less than 9 g. per 100 ml.
2. Overt clinical disease at birth

Stillborn (10–15% all births)

Hydrops foetalis

Not oedematous

We have not considered the significance of previous death due to haemolytic disease, as this is so dependent upon treatment, and at present we believe that there need seldom be more than two deaths in every 100 affected babies born alive.

Method of Assessment

Two three-year periods, throughout which five cases were detected for every 1,000 births, have been taken as control groups, and we consider they represent haemolytic disease as a whole. In the early years (Group A) exchange transfusion was performed in only a few cases, whereas in the later years (Group B) it was used for all babies requiring treatment as assessed on the basis of findings in the cord blood (Walker and Murray, 1954, 1955). It will be seen that the distribution of severity within the two groups is similar (Table I).

TABLE I.—Severity of Haemolytic Disease in Control Groups

Group	Area	Present Pregnancy							
		Total	Stillborn*		Treated		Mild Untreated		
			No.	%	No.	%	No.	%	
A	Northumberland, 1948–50	202	20	10	104	57	78	43	
B	Northumberland and Durham, 1952–4	565	67	12	303	61	195	39	

* Throughout, stillbirths are expressed as a percentage of total births and the varieties liveborn as a percentage of live births.

We then selected separate groups of cases with similar family backgrounds and have compared these one with another and with the control groups as indicated.

Having confirmed the view of Mollison and Cutbush (1949) that the cord haemoglobin level is the most reliable single criterion of severity in this disease, we have used the distribution of cord haemoglobin values as an alternative method for comparing severity in babies with similar preceding histories. It has the advantage of being less dependent on the personal element, so important in clinical observation. We have found the overall pattern of cord haemoglobin values to be remarkably constant and could detect no differences in groups compared year by year or with the total group. The average haemoglobin for each year fell

in the range 13.8–14.4 g. per 100 ml., which corresponds with our observation that in a large community the pattern of haemolytic disease repeats itself.

Aim of Present Study

In this study we have set out to answer the following questions:

1. Is immunization by transfusion of more serious significance than immunization by pregnancy?
2. Have first affected babies only mild disease?
3. Is the severity of disease in subsequent babies related to the severity of the disease in previous babies?
4. Is immunization in an early pregnancy of different significance to that in a later pregnancy, and does the interval between pregnancies modify the prognosis?
5. Is there any relationship between the occurrence of toxæmia of pregnancy and the severity of haemolytic disease?

Summary of Results

In Tables II and III are summarized the results in the principal types of family. Any increase in severity is shown by an increase in the number of stillbirths and by an increase in the proportion of liveborn babies requiring treatment. This may fail, however, to show up variations in the degree of severity among the treated group. Moreover, the selection of cases for treatment is dependent on the criteria of severity adopted. Therefore, in Table III the cord haemoglobin distribution is shown in the same broad categories as Table II.

TABLE II.—Severity of Haemolytic Disease in Relation to Previous History

Previous History	Total	Present Pregnancy					
		Stillborn		Treated		Mild Untreated	
		No.	%	No.	%	No.	%
Rh-positive transfusion	74	6	8	46	68	22	32
First affected babies	853	52	6	455	57	346	43
Subsequent affected babies	396	103	26	219	75	74	25
All cases*	1,323	161	12	720	62	442	38

* We have not included the 13 pregnancies of less than 28 weeks' gestation. These are discussed later.

TABLE III.—Cord Haemoglobin Value in Present Pregnancy in Relation to Previous History

Cord Hb	Rh-positive Transfusion		First Affected Babies		Subsequent Affected Babies	
	No.	%	No.	%	No.	%
>17.7 g./100 ml.	0	Nil	46	10	11	6
14.9–17.7 g./100 ml.	9	39	205	48	67	36
12–14.8 g./100 ml.	7	30	115	27	51	27
9–11.9 g./100 ml.	3	13	42	10	31	17
<9 g./100 ml.	4	18	21	5	27	14
Total	23		429		187	
Stillbirth	6		52		103	
Not determined	45		372		106	
Total No.	74		853		396	

In the period under consideration we determined the cord haemoglobin values in 639 affected babies, and for practical purposes equal numbers fell above and below 14.8 g. per 100 ml., while at the extremes 10% were below 9 g. per 100 ml. and 10% over 17.7 g. per 100 ml.

These haemoglobin values apply only to liveborn babies, and if first affected are compared with subsequent affected cases, depending on whether the haemoglobin level was above or below 14.8 g. per 100 ml., there is a significant increase in severity ($P < 0.01$).

Immunization by Rh-positive Blood Transfusion

Relatively few mothers had been transfused, but in 74 instances we felt reasonably certain that they had received Rh-positive blood. In nine cases this was known and in the remainder it was presumed because each had received at least two bottles of blood of unknown Rh group.

Conflicting views on the significance of immunization by transfusion are held by different workers, but it is fair to point out that calculations have often been based on very small series. Thus Chown (1948) observed no living children after transfusion except in first pregnancies, while Levine *et al.* (1953) and Davies *et al.* (1953) record an increased risk of stillbirth. Mollison and Cutbush (1954) reported a 17% mortality rate in first affected babies following transfusion as compared with 10% in other first affected babies. Allen *et al.* (1950) reported that immunization by transfusion was of similar significance to a history of a preceding erythroblastotic infant, and this opinion is repeated by Vaughan *et al.* (1950) and Diamond (1950).

In our series, 8% of pregnancies ended in stillbirths, while of the babies born alive, 32% were mildly affected and required no treatment (Table II). *There is evidently no increased risk of stillbirth in mothers immunized by transfusion*, but there is a suggestion that the severity of disease in babies born alive is somewhat increased. This apparent increase is best illustrated in the distribution of cord haemoglobin levels as shown in Table III, but it is only when the number of cases needing treatment or the number with cord haemoglobin values of less than 14.8 g. per 100 ml. is combined with the number stillborn that the increase becomes significant ($P = 0.05-0.02$). We therefore believe that the management of mothers developing antibodies should be independent of the means by which immunization was brought about.

Families in which no Previous Baby has had Haemolytic Disease: "First Affected Babies"

When all women immunized by transfusion had been excluded there remained 853 cases with this type of history, subdivided as follows: *Proved first affected*—four babies of primigravidae and 72 babies where the immediately previous Rh-positive baby was Coombs-negative. *Certainly first affected*—351 babies the result of a second pregnancy and where the previous baby was clinically normal. *Clinically first affected*—426 later babies where the previous babies were clinically normal.

The distribution of severity within these groups is shown in Table IV. Cord haemoglobin estimations on 429 of these cases showed that 42% had levels lower than 14.8 g. per 100 ml. and 58% had higher levels. It is of interest that 21 first affected babies had cord haemoglobin values of less than 9 g. per 100 ml.

TABLE IV.—Pattern of Haemolytic Disease in First Affected Babies

Diagnosis	Total	Severity		
		Stillborn	Treated	Not Treated
Proved	76	8%	65%	35%
Certain	351	7%	61%	39%
Clinical	426	5%	52%	48%
All cases	853	6%	57%	43%

It will be seen that the distribution of clinical types is similar in the groups where the evidence that the baby was the first affected in the family is complete or almost complete. In particular, the chance of stillbirth is not far below 10%, and the groups, separately or combined, do not differ from the control groups (Table I). When the clinically assessed cases are considered there is an apparent shift to the milder forms of disease. Fewer babies were stillborn, and of those born alive fewer required treatment. We believe that this has been brought about because some have been preceded by infants with subclinical illness, for we show later that such a sequence does reduce the incidence of severe disease.

Most workers will recall severely ill "first affected" babies, and in fact in the last six months we have seen five such, all born in *extremis*. Their haemoglobin levels ranged from 7.5 down to 3 g. per 100 ml., and their chances of survival, had they been born at home, would have been exceedingly small.

We therefore cannot support the opinion that first affected babies are but mildly affected—and if such a view influences the conduct of the pregnancy, in that the mother is advised against hospital delivery, the baby's life will be risked unnecessarily. We also regard it unwise to tell mothers developing antibodies for the first time, categorically, that there is no risk of stillbirth, for we have been struck by the relative frequency of this outcome as the first manifestation of haemolytic disease in a family.

Severity of Haemolytic Disease when Preceded by an Affected Baby

In Tables II and III we have shown that the severity of haemolytic disease is increased in cases preceded by one or more affected babies. This is apparent because there is a significantly higher incidence of stillbirths in subsequent babies when compared with first affected babies ($P < 0.01$), while subsequent liveborn babies have more serious forms of disease. Significantly fewer survive without treatment, and there is a significant shift towards lower cord haemoglobin values. In relation to each, $P < 0.01$. For one reason or another many mothers who develop antibodies endeavour to avoid large families. Therefore we have considered first in more detail the largest numerical group—that is, the first and second affected babies in a family. There were 192 such families, in 140 of which we had observed each affected baby. The findings are shown in Table V.

TABLE V.—Severity of Haemolytic Disease in First and Second Affected Babies

First Affected Baby	Total of First Babies No. %	Second Affected Baby				
		Mild %	Moderate %	Severe %	Very Severe %	S.B. %
Mild (not treated) ..	49 28	60	30	8	2	4
Moderate	58	25	53	11	11	19
Severe	55 72	17	29	32	22	25
Very severe	10	—	—	75	25	60
S.B.	20 12	—	—	50*	50*	60
Total of second babies ..	192 { No. %	47 32	51 68	29 68	20 68	45 23

* Includes 5 babies, the result of premature induction 35 days before E.D.D.

The overall trend in Table V is towards increased severity in second affected babies. This is not uniform, for the following distinct patterns can be seen: mild disease is very likely to be followed by mild disease; very severely affected and stillborn babies are likely to be followed by stillbirths; moderate and severely affected babies are on average followed by somewhat more serious disease, so that one in four are stillborn.

The number of other cases did not permit us to relate all cases in strict sequence—that is, second to third affected, third to fourth affected, and so on. Therefore we have related all third or later affected babies to their immediate predecessor, and the results are shown in Table VI. These later babies, compared, show only an increase in the number of cases stillborn. This difference is not significant, but we feel that it has been obscured somewhat by the inclusion of many families, which eventually resulted in a succession of several stillbirths. When the later babies in Table VI are compared with the second affected in Table V the increased risk of stillbirth is again apparent, and this time is significant ($P < 0.05$). The other findings in the two tables are similar; therefore we feel justified in relating the severity of disease in any baby to that of its immediate predecessor, and the findings for the total group are shown in Table VII.

For all subsequent affected babies Table VII reveals a 29% risk of stillbirth, which corresponds with Diamond's recent experience (1955, personal communication). Of the babies born alive, 72% will need treatment. An analysis of the cases in groups confirms the small chance of a more mildly affected baby, but suggests that there is almost double the chance of the subsequent baby being similarly rather than more severely affected.

TABLE VI.—*Severity of Haemolytic Disease in Second and Third or Subsequent Pairs of Affected Babies*

Second Affected Baby	Total of Initial Babies		Subsequent Affected Baby				
			Mild %	Moderate %	Severe %	Very Severe %	S.B. %
Mild (not treated) ..	44	25	64	34	—	2	—
Moderate ..	70	—	12	63	25	—	20
Severe ..	47	75	—	34	63	3	25
Very severe ..	11	—	17	33	—	50	45
S.B. ..	64	27	—	13*	74*	13*	77
Total of subsequent babies	236†	No. %	36	66	47	7	80
		%	23	77			34

* Includes 9 babies, the result of premature induction 35 days before E.D.D.

† We have thought it right to include in this table the 32 cases not shown in Table I. They were families in which there was a clear-cut story of two cases of haemolytic disease before 1947.

TABLE VII.—*Relationship of Severity of Haemolytic Disease in Subsequent Affected Babies*

Previous Affected Baby	Total of Previous Babies		Subsequent Affected Baby				
			Mild %	Moderate %	Severe %	Very Severe %	S.B. %
Mild (not treated) ..	93	27	62	32	3	3	2
Moderate ..	128	—	19	57	19	4	20
Severe ..	102	73	9	30	47	13	27
Very severe ..	21	—	10	20	30	40	55
S.B. ..	84	—	—	9*	65*	26*	73
Total of subsequent babies	428	No. %	84	116	76	27	125
		%	28	72			29

* Includes 14 babies, the result of premature induction 35 days before E.D.D.

Study of the various individual groups reveals further points of interest :

1. *Previous Baby Mildly Affected and Surviving Without Treatment.*—Over 60% of these babies are followed by another baby who survives without treatment, and it is exceptional for any requiring treatment (40%) to be more than moderately affected. These proportions are the reverse of those in the complete series. The risk of a following stillbirth is trivial and no worse than in a normal pregnancy. *In fact, the prognosis, once a mother has had a mildly affected baby, is much better than in a person developing antibodies for the first time, in that the next child is almost certain to be born alive, with an excellent chance of survival.*

2. *Previous Baby Having Required Treatment.*—If the previous baby has had a moderate degree of disease there is about a 20% chance of the next baby being stillborn. If born alive, however, only about 1 in 4 will have more severe disease. If the previous baby has had severe disease there is approximately a 25% risk of stillbirth. If born alive 60% will be severely or very seriously affected, and only about 10% will be mildly affected and require no treatment. If the previous baby has had very severe disease the risk of stillbirth is more than 50%, and if liveborn the baby is very likely to have severe disease. In fact, under these circumstances the prognosis is almost as bad as if the previous baby had been stillborn.

3. *Previous Baby Stillborn.*—It will be seen that a previous stillbirth due to haemolytic disease is of grave prognostic import—probably to be followed by another stillbirth or at least by a severely affected baby. We feel that this group merits special and further consideration. Our criteria for diagnosis in these cases have already been described, but, in addition, inquiries have always been made to confirm or exclude common causes of stillbirth other than haemolytic disease. One major difficulty is that cord blood is seldom taken from these cases and serological proof is often missing. However, a preliminary analysis depending on whether the preceding stillbirth was proved, certain, or probable revealed similar results, so we have pooled all cases for the purpose of this account.

Significance of History of Previous Stillbirth

In Table VIII are shown the results in pregnancies preceded by one or more stillbirths due to haemolytic disease, and for comparison we show the results in pregnancies preceded by stillbirth thought to be due to other cause. The latter cases did not include families in which the stillbirth occurred in a first pregnancy or in which it was followed by a normal Rh-positive baby.

TABLE VIII.—*Significance of History of Previous Stillbirth*

Previous Pregnancy*	Present Pregnancy						
	Stillborn		Treated		Mild Untreated		Total
	No.	%	No.	%	No.	%	
S.B. due H.D.N.	41	62	2†	100	—	—	66
> 1 S.B. due H.D.N.	17	68	8†	100	—	—	25
All S.B. due H.D.N.	58	64	33	100	—	—	91
S.B. due to other cause	6	11	34	72	13	28	53

* No families have been included twice in this table; they appear either as "one" or as "more than one" previous stillbirth.

† Includes 11 babies following premature induction.

Table VIII confirms that a stillbirth due to haemolytic disease is likely to be followed by a similar occurrence in later pregnancies, whereas stillbirth from other cause is not of significance ($P < 0.01$). It does not reveal the full serious import of a previous stillbirth due to haemolytic disease, for although we have shown 12 abortions following stillbirth we have not included them in the calculations, even though we regarded them as due to haemolytic disease. If they are included, the chance of a live birth is reduced to 31%. Further, it must be kept in mind that many of the babies born alive were severely affected, and in fact six of our cases were moribund at birth and in reality "near hydrops."

A factor which may have modified our results is that a third of the living babies included in Table VIII were the result of premature induction. For the past two years this has been performed 35 days before the E.D.D. in families with a history of stillbirth due to haemolytic disease and where the father was homozygous Rh positive. The results of this inquiry and a more detailed study of the problem of stillbirth in haemolytic disease will be reported elsewhere, because we feel this remains the outstanding problem in this disease. Our analysis two years ago, before adopting premature induction, is therefore relevant.

At that time 30 out of 45 pregnancies following one stillbirth ended similarly, while 18 out of 24 with more than one preceding stillbirth ended in this way. If abortions were included the risk of intrauterine death was 70% after one stillbirth and 80% after more than one stillbirth.

All mothers immunized by transfusion were excluded from this analysis, but it is of interest that in five instances mothers immunized by transfusion had a stillbirth followed by a further pregnancy. Three resulted in stillbirth and two in live babies. By coincidence there was a sequence of Rh-positive blood transfusion, stillbirth from other cause, and subsequent pregnancy also in five cases. All five babies were born alive, but all needed treatment.

It is reasonable to consider whether the outlook is different in a family starting with a "first affected" stillbirth as compared with a family where stillbirth first occurs following liveborn affected babies. We were unable to demonstrate any difference in these two groups; in fact, 18 families had liveborn affected babies before stillbirth, and in each another stillbirth occurred.

Previous History of Kernicterus

Kernicterus is one of the most striking and distressing features of haemolytic disease. It is nearly always fatal, and many regard it as of bad prognostic significance in regard to subsequent pregnancies.

In 21 of our families a previous baby had died and at necropsy was found to have kernicterus, while in 19 additional cases a confident clinical diagnosis of kernicterus had been made. The results of the next pregnancy in these families is shown in Table IX. The risk of stillbirth was

TABLE IX.—*Significance of a Previous History of Kernicterus*

No.	Stillborn	Liveborn	
		Needing Treatment	Mild Untreated
40	6 (15%)	31 (91%)	3 (9%)

not increased, but the severity of disease in babies born alive was similar to that seen following all severe forms of disease. Out of the 34 babies born alive, 33 survived, all without sequelae, but 29 out of the 31 needing treatment received early exchange transfusion. The fatal case, that of a baby born during the time of the "national trials," was selected for "simple transfusion" and died from kernicterus without anaemia having occurred.

It is clear that a previous history of kernicterus does not warrant a bad prognosis being given. Most subsequent babies will meet our cord blood criteria for exchange transfusion, so one could not raise serious objection to the use of a previous history of kernicterus itself as an indication for exchange transfusion. With this treatment the prospect for the baby is excellent.

Previous History of Abortion

Although there was a history of abortion in 165 families we have considered only those families in which it was known whether abortion had occurred before or after immunization. The differences between these families are shown in Table X. The numbers are small, but if the

TABLE X.—*History of Abortion in Relation to Immunization and Result*

Previous History	Total	Present Pregnancy			
		S.B.	Abortion	Liveborn	
				Treated	Not Treated
Abortion before immunization	35	17%	—	62%	38%
Abortion after immunization	15	46%	13%	72%	28%

stillbirths and abortions are considered jointly the outlook is bad if an abortion has occurred following immunization. The pattern in mothers in whom abortion occurred before immunization, however, is the same as for the control groups. This suggests that abortions may be due to haemolytic disease, and, if so, their significance in relation to subsequent babies is similar to that of stillbirth due to haemolytic disease.

Cord Blood Levels in Subsequent Affected Babies

So far we have considered the relationship between successive cases of haemolytic disease based on a comparison of clinical pictures. It remains to be seen whether the conclusions reached can be confirmed by comparing the clinical picture in one baby with the cord blood level in its successor.

TABLE XI.—*Relationship of Clinical Type to Cord Haemoglobin in First and Second Affected Babies*

First Affected Baby	Total	Second Affected Baby				
		Cord Haemoglobin Level (g. per 100 ml.)				
		<9	9-11.9	12.0-14.8	14.8-17.7	>17.7
Mild ..	29	—	3	9	17	—
Moderate ..	22	2	3	9	7	1
Severe ..	27	2	8	11	6	—
S.B. ..	4	3	1	—	—	—
Total ..	82	7	15	29	30	1
		51 (62%)			31 (38%)	

Haemoglobin.—Table XI shows this relationship for first and second affected babies. If a comparison is made between first and second affected babies, taking a cord haemoglobin value of 12 g. per 100 ml. as the dividing line, a correlation between lower haemoglobin values and a history of previous stillbirth or severe disease can be shown statistically ($P < 0.01$). So far increased severity in later babies has usually been shown by the occurrence of an increased number of stillbirths and by a suggestive increase in severity of clinical disease in the babies born alive. Therefore in Fig. 1 we have plotted the haemoglobin values in 68 consecutive babies one against the other. On occasions when haemoglobin estimations have been performed on more than two babies in one family each has been plotted against its immediate predecessor, so might appear on one axis when related to an older sibling and on the other when related to one younger. Plotted in this manner, two identical haemoglobin levels fall on the diagonal, whereas a lower haemoglobin in a later baby would appear below the diagonal and a higher one above.

FIG. 1.—The lines drawn parallel with the diagonal represent ranges of 10% and 40% haemoglobin value above and below the observed reading.

Bilirubin.—In Fig. 2 the bilirubin levels in 47 pairs of consecutive babies are shown in a similar way. The overall distribution of haemoglobin and bilirubin values is similar for preceding and later babies. Many differences are small in degree, only half of the cases showing a change of more than 10% haemoglobin or 1 mg. of bilirubin. When a change of this degree did occur there was double the chance of the baby being more severely rather than less severely affected. Only a few cases showed extreme variations, and these were as likely to be more mildly as more severely affected.

FIG. 2.—The lines drawn parallel with the diagonal represent a range of bilirubin value of 1 mg. per 100 ml. above and below the observed reading.

Does Immunization in an Early Pregnancy Modify the Prognosis?

Our observations on this point are based on the four years 1947-51, and we present the findings in 362 families in which we felt sure of the time of onset of immunization. Only severity of disease in the first affected baby is considered (Table XII).

The numbers of cases in individual pregnancies are too small to permit formal statistical comparisons between each. Therefore we have made a comparison between first and second pregnancies combined *versus* all later pregnancies. We have taken stillbirths together with babies requiring treatment as representing severe disease. Only in this way

were we able to demonstrate a small increased risk of severe disease if immunization occurred in an early pregnancy ($P = 0.05-0.02$).

TABLE XII.—*Severity of Disease in First Affected Babies Related to Parity*

No. of Pregnancy Resulting in First Affected Baby	Total	Severity of Disease in First Affected Baby		
		S.B.	Requiring Treatment	Mild Untreated
1st	4	—	3	1
2nd	169	19	102	48
3rd	98	6	60	32
4th	52	2	29	21
5th	21	2	9	10
6th	3	1	2	—
7th	5	—	3	2
8th	2	—	2	—
9th or later ..	8	1	—	7
Total	362	31 (8%)	210 (63%)	121 (37%)

Is Prognosis Modified by the Interval between Pregnancies ?

We considered 169 mothers in whom the disease was first evident in the second pregnancy. This is the largest group in our material and the only one for which we know precisely the period over which the immunizing pregnancies were spread. We were unable to demonstrate any difference in the severity of disease, depending upon the number of years between the two pregnancies.

It remains to be considered whether, once immunization has occurred, the interval between pregnancies modifies the severity of disease in subsequent affected babies. Table XIII shows the severity of disease in second affected babies in

TABLE XIII.—*Severity of Disease. In Relation to Interval Between First and Second Affected Baby*

Interval Between First and Second Affected Babies	Total	Second Affected Baby		
		S.B. %	Treated %	Mild Untreated %
3 years	113	22	66	34
>3	76	25	77	23
Total No.* ..	189	44	102	43

* Three cases are not recorded.

relation to the number of years between the first and second affected babies, and compares cases occurring in three years with those occurring over a longer period. Obviously there is no real difference between these groups, though there is a suggestion that a longer interval between affected babies worsens the prognosis. This is in agreement with Stratton (1955), but contrary to widely held beliefs. Analyses, using different intervals for comparison, revealed no relationship between the severity of disease and spacing of pregnancies.

Is There Any Family Pattern ?

So far we have only considered how the occurrence and severity of preceding haemolytic disease alters the prospect for the next baby. It remains to be shown whether such factors combine to produce distinctive family patterns. For this purpose we have studied 58 families in which we had personally observed all cases. There were 37 with three affected babies, 17 with four, 3 with five, and 1 family with six affected babies. The patterns seen were as follows:

All mild untreated	8 families
First mild, remainder requiring treatment	10 "
All liveborn but requiring treatment ..	13 "
One or more liveborn babies followed by a succession of stillbirths	10 "
All stillborn	7 "
No pattern discerned	10 "
	58 "

The first affected baby was born alive in 50 of the 58 families, but the final baby in only 34 instances, and three of these

followed premature induction. In almost half of the families at least one stillbirth occurred; this is in contrast to Davies *et al.* (1953), who found that three-quarters of their families had no stillborn baby. Their finding was probably due to the fact that they considered many families with only two affected babies, for they estimated the risk of stillbirth in second affected babies at 20%, but in third affected at 40%, which corresponds with our observations.

We feel that consideration of the family pattern adds little to judgments based on the form of disease in the preceding baby, although where there has been a similar outcome in two or more preceding babies repetition in any future pregnancy is probable. In a small minority of families the severity of disease is not as expected, and in these families further predictions are similarly apt to be wrong.

Other Factors Possibly Modifying Severity

The risk of immunization to the Rh factor is known to be greater when the father is compatible with the mother within the ABO groups, and this was confirmed. We further considered whether compatibility might also modify the severity of disease once immunization had occurred, but we could not demonstrate any relationship between the ABO groups of mother, father, or child and severity.

The interspersing of the family with normal Rh-negative babies did not alter the prognosis for subsequent pregnancies—for example, the risk of stillbirth following stillbirth was still about 80% even when there were one or more Rh-negative babies subsequent to the first hydropic foetus.

Toxaemia.—We have classified as toxæmic any patient with a blood pressure of 140/90 or higher occurring after the twentieth week of gestation. There were 77 mothers with toxæmia of this degree, and the pregnancies resulted as follows: stillborn, 30 (39% of total births); requiring treatment, 26 (55% of live births); mild untreated, 21 (45% of live births). The total incidence of toxæmia in the immunized Rh-negative mothers is 5%, which is the same as the overall incidence of toxæmia in the hospitals concerned. There is, however, a significant increase in the proportion of stillbirths. It might be that toxæmia and the presence of antibodies, either of which may cause stillbirth, would in combination increase this risk. Alternatively, one could postulate that the large abnormal placenta associated with hydrops foetalis could itself be causal. Although it is uncertain which is cause and which is effect, it seems that the occurrence of toxæmia in an immunized mother should be regarded as indicating an increased risk of stillbirth.

Discussion

In the introduction an indication has been given regarding the conflicting views expressed about the relationship of previous history and severity of disease in later infants. The assessment has often been in terms of mortality, which, although a valid yardstick for a particular homogeneous series, being so dependent on treatment, precludes comparisons between different series. Many reported series are small, and, unless representing the complete range of disease within a community, must in varying degrees be "selected."

Diamond (1950) stressed increased severity in later babies because of a statistically significant increase in stillbirths, an increased number of deaths, and a decrease in the mild forms of the disease. Many other authorities, both before and since that time, have concurred in this view either by showing a better prospect for a first affected child (Allen *et al.*, 1950; Vaughan, 1951; Mollison and Cutbush, 1954) or a worse prognosis in later babies (Potter, 1948, 1953; Allot, 1951). We, too, can confirm that statistically there is a general trend towards more severe disease, but we have tried to demonstrate that the pattern of increasing severity is not uniform in all cases. Two points stand out clearly: that once a stillbirth has occurred due to haemolytic disease there is a very high risk that all subsequent Rh-positive babies in that family will also be stillborn; and that any baby mildly affected and not requiring treatment is

unlikely to be followed by a stillbirth, but, most often, will be followed by a baby with similar mild disease. On this last point we differ from Levine *et al.* (1953), who felt that mild untreated disease should not be overlooked, as it was apt to be succeeded by severely affected perhaps hydropic cases. They also expressed the view that first affected babies would have only mild disease. We were unable to confirm this, for in our series about 10% of first affected babies were stillborn, and nearly 60% of those born alive needed treatment. These findings are not merely of academic interest, for they mean that a mother developing antibodies for the first time should not be treated any differently from one who has already had affected infants. In particular, she should be urged to accept hospital delivery, and should not be told that there is little risk to the baby.

The pattern of increasing severity with each pregnancy is not inevitable in every family, and exceptions with mild cases following severe or even stillborn babies have been noted (Chown, 1948; Allot and Holman, 1949; Zuelzer, 1948). We agree that individual exceptions do occur, but believe that, if the severity of the preceding case is assessed in clinical terms rather than on survival, the exceptions are relatively few. We think that for a long while yet we shall sometimes have to rely on a retrospective clinical assessment of the previous obstetrical history, and suggest that, where a history diagnostic of haemolytic disease exists, it should be borne in mind that this probably represents severe disease with a corresponding worse prognosis. It is our experience that very ill or stillborn babies are clearly remembered, whereas minor varieties of disease are easily forgotten or missed. We analysed 283 cases born between 1947 and 1951—depending on whether the diagnosis of previous disease was certain as based on serological proof or a diagnostic clinical picture, or whether the evidence for previous haemolytic disease was only probable. The outlook was similar in the groups where the previous history of the disease was only probable and where it was proved serologically. Where, however, the previous baby had a diagnostic clinical picture of the disease, such families had a worse prognosis, there being an increased risk of stillbirth, from 28% to 43%, and a fall, from 33% to 16%, in the number of babies surviving without treatment.

Chown *et al.* (1953) estimated that there was a 10% chance of a mild untreated case following a very severely affected baby, but we believe that a spontaneous live birth following a stillborn or very severely affected baby is a rarity and have never seen mild disease under these circumstances.

Unlike Davies *et al.* (1953), we were not able to demonstrate clear-cut family patterns. We found that the most reliable prognostic guide is based on the outcome in the immediate predecessor, although where two or more preceding infants have had similar disease the likelihood is that the next baby will also be similarly affected.

Because kernicterus is the feature of haemolytic disease that has caught the public imagination we would stress that a previous history of kernicterus carries no worse prognosis than the previous occurrence of any liveborn variety requiring treatment. There are many families in which one baby has died from kernicterus and a later baby treated by early exchange transfusion has survived and developed normally.

Finally, we could find no evidence for giving a worse prognosis to mothers immunized by transfusion or by an early pregnancy, nor any reason for advising mothers to leave several years between pregnancies.

Summary and Conclusions

A study of the previous history has been made of 1,033 immunized Rh-negative mothers in Northumberland and Durham for the period 1947–55. The total of 1,336 babies with haemolytic disease represents an incidence of 5 cases for every 1,000 births during this period, and is, we believe, representative of the whole range of

haemolytic disease of the newborn. Cases with similar backgrounds have been grouped together and compared with control series. From this experience we have found that:

1. Immunization by Rh-positive blood transfusion is of similar significance to immunization by pregnancy.
2. Where there has been no previous affected baby the risk of stillbirth is about 10%, but of those born alive 40% will not require treatment.
3. Although statistically there is a general trend towards more severe disease in succeeding pregnancies, this pattern of increasing severity is not uniform for all cases. Distinct family patterns are relatively rare, but considerable help in estimating the probable outcome of a given pregnancy can be obtained from the form and severity of the disease in the immediate preceding baby. This relationship can be expressed as follows: (a) Where the previous infant was mildly affected and did not require treatment, the risk of stillbirth is no more than 2%, and of those born alive 60% will survive without treatment. (b) The previous occurrence of kernicterus does not imply a more serious outlook than that of any previously affected infant requiring treatment. (c) If a previous baby was stillborn from haemolytic disease, there is about an 80% chance that the next baby if allowed to go on to a spontaneous delivery will also be stillborn. If born alive it will certainly have severe disease and require treatment.
4. Immunization from an early pregnancy was only slightly more serious than immunization from a later pregnancy. The time interval between affected babies did not materially affect the prognosis.

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REFERENCES

- Allen, F. H., jun., Diamond, L. K., and Vaughan, V. C. (1950). *Pediatrics*, **6**, 441.
- Allot, E. N. (1951). In *Modern Trends in Paediatrics*, edited by Sir L. Parsons. London.
- and Holman, C. A. (1949). *Lancet*, **1**, 210.
- Chown, B. (1948). *Blood*, Special issue, No. 2, p. 155.
- Allen, F. H., jun., and Mollison, P. L. (1953). "Erythroblastosis Fetalis" in the Report of the Seventh M. & R. Pediatric Research Conference.
- Davies, B. S., Gerrard, J., and Waterhouse, J. A. H. (1953). *Arch. Dis. Childh.*, **28**, 466.
- Diamond, L. K. (1950). In *Mitchell-Nelson Textbook of Pediatrics*, edited by W. E. Nelson. Philadelphia and London.
- Ellis, R. W. B. (1951). *Disease in Infancy and Children*. Edinburgh.
- Levine, P., Vogel, P., and Rosenfield, R. E. (1953). *Advanc. Pediat.*, **6**, 97.
- Mollison, P. L., and Cutbush, Marie (1949). *British Medical Journal*, **1**, 123.
- (1954). In *Recent Advances in Paediatrics*, edited by D. Gairdner. London.
- Potter, E. L. (1948). *Pediatrics*, **2**, 369.
- (1953). "Erythroblastosis Fetalis" in the Report of the Seventh M. & R. Pediatric Research Conference.
- Sheldon, W. (1955). *Diseases of Infancy and Childhood*, 7th ed. London.
- Stratton, F. (1955). In *Modern Trends in Haematology*, edited by J. F. Wilkenson.
- Vaughan, V. C. (1953). "Erythroblastosis Fetalis" in the Report of the Seventh M. & R. Pediatric Research Conference.
- Allen, F. H., jun., and Diamond, L. K. (1950). *Pediatrics*, **6**, 706.
- Walker, W., and Murray, S. (1954). *British Medical Journal*, **2**, 126.
- (1955). Report on Haemolytic Disease of the Newborn to the Northern Regional Hospital Board.
- Whitby, L., and Newns, G. H. (1953). In Garrod, Batton, and Thursfield's. *Diseases of Children*, 5th ed., edited by A. Moncrieff and P. Evans, vol. 2. London.
- Zuelzer, W. W., Wheeler, W. E., and Leonard, M. F. (1948). *Pediatrics*, **1**, 799.