and the police officers assigned to the case; the directors of Boots Pure Drug Co. Ltd., Nottingham; Dr. D. K. Bruce, medical superintendent, Storthes Hall Hospital, near Huddersfield; Professor C. S. Russell, department of obstetrics and gynaecology, Sheffield University; Professor R. H. S. Thompson, department of chemical pathology, Guy's Hospital Medical School; and Mr. T. Dean, consultant obstetrician and gynaecologist, Barnsley Group of Hospitals.

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CASE FOR INDUCTION OF LABOUR IN TREATMENT OF HAEMOLYTIC DISEASE OF THE NEWBORN

BY

G. A. KELSALL, M.B., Ch.B.

G. H. VOS

King Edward Memorial Hospital for Women, Subiaco,
Western Australia

AND

R. L. KIRK, M.Sc.

Zoology Department, University of Western Australia

In a series of papers in the *British Medical Journal*, Walker and his colleagues have reported their experience in the management of cases of haemolytic disease of the newborn (Walker and Murray, 1954, 1956; Walker, Murray, and Russell, 1957; Walker and Neligan, 1955). Their analysis has been based largely on a series of cases referred for treatment in the Newcastle United Hospitals and in other centres in N.E. England during the past ten years. The management of the cases reported in those studies has been modified in the light of experience, so that the earlier reports refer to methods of treatment rather different from those used currently.

In the initial studies Walker and his colleagues subscribed to the view that the induction of labour had no place in the treatment of the infant suffering from haemolytic disease of the newborn. This view was based largely on the results of a clinical trial which suggested that prematurity greatly increased the risk of death in affected infants (Mollison and Walker, 1952; Armitage and Mollison, 1953). More recently, however, the Newcastle group has suggested that induction of labour should be used in cases where an Rh-immunized mother has already had a stillbirth due to

Rh incompatibility in a previous pregnancy. This suggestion has been incorporated in the second edition of *Blood Transfusion in Clinical Medicine* (Mollison, 1956). Subsequently, as a result of a study of the influence of the father's genotype on the severity of haemolytic disease in the affected infant, Murray (1957) has suggested that induction of labour might be justified also in cases where the father is shown to be R_2R_2 (cDE/cDE), since the risk of stillbirth in such cases, according to her analysis, is much greater than if the father is of any other Rh genotype.

In contrast to the views of the English workers, we have during the past seven years consistently advocated the use of induction of labour as an integral part of the treatment of Rh cases where the antenatal indications suggest that the infant will be severely affected. We believe that the time is now ripe to attempt a detailed comparison of the work of both the English group and our own.

Criteria of Severity

Indications for Exchange-transfusion

Walker and Murray (1954), as a result of several years' experience, have adopted the following criteria for determining the need for exchange-transfusion: "A Coombs-positive baby with a cord Hb level of 14.8 g.% or less, and a cord Hb level of 14.9 to 17.7 g.% associated with a bilirubin level greater than 2.7 mg. per 100 ml. . . . In those cases in which the cord-blood samples were not ideal we have been guided by whichever result was available. In practice this has usually been the cord bilirubin level, and we have treated any infant with a value greater than 2.7 mg. per 100 ml. . . . If cord-blood values were not available we have relied on clinical criteria."

Our practice during the past six years has been to rely upon the antibody level in the maternal serum as determined by a carefully standardized indirect antiglobulin method (Kelsall and Vos, 1952; Watson and Vos, 1952; Kelsall, Vos, Kirk, and Shield, 1957). No baby receives treatment if the maternal indirect antiglobulin titre at term is 1/64 or less. On the other hand, we exchange-transfuse all infants where the maternal indirect antiglobulin titre at term is higher than 1/128. Our original procedure was to transfuse all infants where the maternal titre at term was 1/128. We have found more recently, however, that some infants in this category with a high cord-blood haemoglobin value and no excess antibody free in the cord serum can safely be left alone.

Indications for Induction of Labour

In order to justify the premature termination of a pregnancy some reliable criterion must be available for predicting the severity of the disease in the infant. Since at the present time no complete certainty is associated with any of the criteria used for assessing severity in Rh cases we have to rely on a statistical evaluation of whatever criterion is being considered.

Walker and Murray (1956) have shown that when a mother has had one or more stillborn infants due to Rh incompatibility the chance of stillbirth in the next Rh-positive pregnancy is approximately 80%. A previous stillbirth is suggested, therefore, as a sufficiently reliable indication to justify induction of labour in the next pregnancy.

This criterion of severity, though perfectly valid, has the disadvantage that the mother must experience at least one stillbirth in order to provide the yardstick for prognosis in the next pregnancy. In addition there are many cases where the mother has had a seriously affected but surviving child in which the chances of a stillbirth in the next pregnancy are quite high. Walker and Murray have shown for their own series that if the previous baby was very severely affected the chance of a stillbirth is almost as high as when the previous pregnancy ended in a stillbirth, and that even when

the previous baby was severely affected the chance of a still-birth is still 25%. In a more recent but still preliminary study Walker (1957) has explored the use of spectrophotometric analysis of samples of amniotic fluid obtained by abdominal paracentesis. He reports that specimens obtained at the 32nd week of pregnancy can be used to forecast correctly an affected child in approximately 90% of cases, and suggests that this method may be of value in discriminating between an Rh-negative and an Rh-positive foetus in cases where a woman married to a heterozygous husband has had a previous stillbirth.

We believe that it is desirable to use a criterion of severity which is applicable in the absence of a previous stillbirth and also during the first pregnancy in which Rh antibodies are present in the mother. For this reason, since 1950 we have assessed the need for induction of labour, as we have the need for exchange-transfusion, using the indirect antiglobulin titre of the maternal serum. Our practice in general is to recommend induction at the 35th or 36th week of pregnancy when the maternal antiglobulin titre is at 1/512 or higher, and at the 37th or 38th week when the titre is at 1/128 or 1/256. A maternal titre of 1/64 or less does not merit the artificial termination of pregnancy.

Reliability of Antiglobulin Titre as a Prognostic Index

From October, 1951, to April, 1957, we have observed 429 infants which have resulted from 421 consecutive pregnancies where Rh antibodies were detected in the mother's serum. A further series of 69 cases between January, 1950, and October, 1951, have been analysed in part previously (Kelsall and Vos, 1952). These early cases were accumulated during the exploratory period in this investigation; treatment was not consistent throughout, and they have therefore been excluded from the present discussion. Kelsall *et al.* (1957) have analysed in detail the first part of the series of cases reported here.

From October, 1951, we have attempted to follow our standard rules for the management of the cases as closely as possible, although we have not always been able to do this. All antibody titrations have been carried out in the same laboratory, using the same procedure, and 96% of the exchange-transfusions have been performed by the same operator (G. A. K.). All cases have been included where an antiglobulin titration of the mother's serum was carried out either on the day of birth or within two or three days prior to birth and where the pregnancy continued for at least 20 weeks. In 265 cases weekly or fortnightly antiglobulin titrations were carried out over at least the last ten weeks of pregnancy: 43 of these pregnancies resulted in Rh-negative infants. In the remaining cases, for various reasons, titrations could be carried out only sporadically throughout pregnancy, or near term.

Of the total of 429 infants, 56 (13.0%) were Rh negative. Of the remaining 373 incompatible infants, 65 (17.4%) were stillborn and 308 (82.6%) were liveborn. Thirty-four of the liveborn infants (9.1% of the incompatible infants) subsequently died, 20 of them despite prompt and adequate exchange-transfusion. The other 14 were untreated, death

having supervened before exchange-transfusion could be started. Four of these untreated infants were of 30 weeks or less gestation.

Table I shows the distribution of these cases by the indirect antiglobulin titre of the mother's serum at term. The foetal wastage from all causes rises from 1.7% where the maternal titre is 1/64 or less to 63.4% where the titre is 1/2,048 or higher. Infants born to mothers with titres of 1/64 or less, with the exception of four cases, received no treatment. All viable infants, with the exception of 13 cases, born to mothers with titres of 1/128 or higher were exchange-transfused. The four cases which were exchange-transfused where the maternal indirect antiglobulin titre at term was 1/64 or less were transfused because of over-anxiety by the patient's doctor. There is nothing to suggest that they would not have survived normally if they had been left untreated.

Almost all of the foetal wastage in this series occurred in cases where the maternal antiglobulin titre at term was 1/512 or higher. The remaining cases, although indicating that stillbirth or neonatal death may occur where the maternal titre is lower than 1/512, have to be considered in the light of the actual causes of death. Of the four stillbirths in the lower-titre categories, two at least were not due primarily to Rh incompatibility, one being a mongol and the other an anencephalic monster. There were six neonatal deaths in the same titre categories. One of these was of only 29 weeks' gestation, was untreated, and died primarily of prematurity; another died at the age of 4 days with an obstruction of the duodenum, whilst one died at home aged 3 weeks, the diagnosis of the cause of death being septicaemia. Thus of the 10 cases where a stillbirth or a neonatal death resulted if the mother had an antiglobulin titre at term of less than 1/512, only five were due primarily to Rh incompatibility. This means that in this series, with our methods of treatment, 95% of the foetal wastage due to Rh incompatibility occurred in mothers with an indirect antiglobulin titre at term of 1/512 or higher.

Any criterion of severity based on neonatal wastage will be dependent on the effectiveness of the exchange-transfusion therapy. If no therapy had been given the number of deaths would have been much higher. It is possible, however, to test the value of indirect antiglobulin titre at term as a measure of severity in another way. We have shown previously (Kelsall *et al.*, 1957) that there is a highly significant

TABLE II.—Relationship Between Maternal Indirect Antiglobulin Titre at Term and Cord-blood haemoglobin values for Rh-positive Infants Born to Rh-immunized Mothers

Cord-blood Hb (g./100 ml.)	No. of Cases at Maternal Titre of:						All Titres
	1/64 or Less	1/128	1/256	1/512	1/1,024	1/2,048 or Higher	
18.0 and over	7	1	3				11
16.0-17.9 ..	11	7	6	4	1	1	30
14.0-15.9 ..	24	9	23	16	9	3	84
12.0-13.9 ..	6	6	14	18	8	3	55
10.0-11.9 ..	2	1	6	11	9	5	34
8.0-9.9 ..				4	10	11	25
6.0-7.9 ..			1	1	6	5	13
5.9 and less				1	6	7	14
Total ..	50	24	53	55	49	35	266
Not available	9	5	5	11	6	6	42

TABLE I.—Distribution of 373 Cases of Incompatible Infants Born to Rh-immunized Mothers from October, 1951, to April, 1957, by Maternal Indirect Antiglobulin Titre at Term

Maternal Titre at Term	No. of Cases	Liveborn Rh + Infants		Stillbirths	% Foetal Wastage
		Survived	Died		
1/64 or less ..	60	59	0	1*	1.7
1/128 ..	30	28	1	1†	6.7
1/256 ..	60	53	5	2	11.7
1/512 ..	70	62	4	4	11.4
1/1,024 ..	82	46	9	27	43.9
1/2,048 or over	71	26	15	30	63.4
All titres ..	373	274 (73.5%)	34 (9.1%)	65 (17.4%)	

* Mongol. † Anencephalic monster.

correlation between the maternal indirect antiglobulin titre at term and cord-blood haemoglobin values ($r = -0.612$). The relationship between maternal titre and cord-blood haemoglobin for the 266 cases of the present series of liveborn Rh-positive infants where the relevant information is available is shown in Table II.

Two points of interest emerge from a consideration of the distribution of these cord-blood haemoglobin values. The first is that the cases in our series are more severe than those reported by Walker and Murray (1954). For the two years 1952 and 1953, 30% of their cases had cord haemo-

globin values of less than 13.3 g. per 100 ml. In our series 53% had haemoglobin values of 13.9 g. per 100 ml. or less (44% were actually less than 13.3 g. per 100 ml.). Allowance for this difference in severity must be made when comparing either the percentage of cases requiring exchange-transfusion or the success of the treatment in the two series.

Secondly, it is clear that there is a considerable area of overlap in the infants which Walker would consider to require exchange-transfusion and those which would receive it by applying our rules. Fifty-nine of our Rh-positive infants required no treatment (although, as noted above, four of these received it) since the maternal antiglobulin titre at term was 1/64 or less. In addition treatment was withheld from a further 10 infants with a maternal titre of 1/128 largely on the basis of absence of excess antibody in the cord serum at term. In total, therefore, at least 69 out of 308 liveborn Rh-positive infants (22.0%) survived without treatment. It is interesting to note from a study of the individual Hb values that at least 29 of these had a cord-blood haemoglobin of 14.8 g. per 100 ml. or less and would have been exchange-transfused by the English workers.

On the other hand, two of our cases which were exchange-transfused had a cord haemoglobin value above 17.7 g. per 100 ml. and would not have been exchange-transfused on the English standard. In addition, 40 of our exchange-transfused cases fell into the intermediate category where a bilirubin estimation would be necessary on the English standard. We have extracted the bilirubin values from our records for the cases with cord Hb values of 14.8–17.5 g. per 100 ml. in the titre categories of 1/128 or higher. Thirty-three of these had bilirubin determinations, and 15 of them were lower than 2.7 mg. per 100 ml. in the cord serum. Thus at least 17 of our cases which were exchange-transfused would not have merited exchange-transfusion on the English standard at birth, though some of these may have required either exchange or simple transfusion later on if severe jaundice developed after birth.

It is interesting to note, therefore, that the two sets of criteria employed as an indication for exchange-transfusion—maternal indirect antiglobulin titre on one hand, and a combination of cord-blood haemoglobin and bilirubin values on the other—have about the same efficiency in predicting the need for exchange-transfusion.

Titre Level and Duration of Response During Pregnancy

Although there is a close relationship between the maternal indirect antiglobulin titre at term and the chance of having a successful outcome of pregnancy, this by itself does not mean necessarily that the early induction of labour should be carried out. If the maternal titre at 36 weeks is 1/512, it could be argued that it might remain at this level during the next four weeks. The relationship between maternal indirect antiglobulin titre at delivery and outcome shown in Table I would indicate the chance of successful outcome in such a case to be greater than 90%. But the picture obtained by considering the relationship between a single maternal indirect antiglobulin titration at term and chance of survival may be misleading. It does not indicate whether the titre determined at the time of delivery has just arrived at that level, perhaps quite suddenly from a low or zero value, or whether the foetus has been exposed to the same quantity of antibody for a considerable length of time.

In 222 of our incompatible cases antibody titrations have been carried out weekly or fortnightly during the last 10 weeks of pregnancy. This has made possible the calculation of a "titre index" to give some measure of the effect of the titre level and the duration of the response on the severity of the disease in the affected child. The titre index is calculated by multiplying the titre code number by the number of weeks and summing for the total 10-weeks period. The code numbers used range from 1 for a titre of 1/16 or less, 2 for 1/32, 3 for 1/64, etc., to 9 for a titre of 1/4,096 or higher. Thus a mother who has maintained a titre of 1/1,024 over

the whole 10-weeks period will have a titre index of $7 \times 10 = 70$. On the other hand, a mother who has a titre of 1/1,024 at term but started the 10-weeks period with a titre of 1/64 and rose progressively each two weeks up to this titre will have an index of $2 \times 3 + 2 \times 4 + 2 \times 5 + 2 \times 6 + 2 \times 7 = 50$.

The distribution of our 222 cases in four categories of titre index where this information is available is given in Table III. Where the titre index is 40 or less, as it was in

TABLE III.—*Relationship Between Maternal Indirect Antiglobulin Index and Outcome of Pregnancies of Rh-sensitized Mothers. See Text for Method of Calculating the Index*

Indirect Antiglobulin Index	No. of Cases	Liveborn Rh + Infants		Stillbirths	% Foetal Wastage
		Survived	Died		
40 or less ..	87	84	2	1*	3.4
41–60 ..	71	54	8	9	23.9
61–70 ..	39	16	3	20	59.0
71 and over ..	25	5	4	16	80.0
All indexes ..	222	159	17	46	28.4

* Mongol.

87 of the cases (39%), the chance of a fatal outcome is only 3.4%. The one stillbirth was the mongol referred to previously. If the titre index is between 41 and 60 the chance of a fatal outcome is 23.9%, and from 61–70 it is 59.0%. If the titre index is above 70, as it was in 25 of our cases, the chance of a fatal outcome is 80%.

On the basis of these results it is possible to estimate the increase in severity which will occur if a pregnancy is allowed to continue for any particular length of time. For example, if a mother has reached 36 weeks and has a titre of 1/1,024, and during the previous six weeks her titre score has reached 40, then even if her titre remains unchanged she will accumulate $4 \times 7 = 28$ points to give a final titre index of 68 if the pregnancy continues to full term. This means that there is almost a 50% chance that the infant will be stillborn, or, if liveborn, will be very seriously affected, with a 30% chance of death. In some of the liveborn cases death will occur before exchange-transfusion can be started. It is clear, therefore, that accurate knowledge of the maternal antibody level and its behaviour from the 26th week of pregnancy onward enables one to predict before birth the degree of severity in the affected child with a high degree of accuracy.

Two factors at present complicate the use of the indirect antiglobulin titre and index as prognostic tools, though neither reduces its value when used with care. The first complicating factor is that even though a high titre index may be obtained, owing to the persistence of antibodies from a previous pregnancy, an Rh-negative infant may result. Out of 43 cases in the present series where the outcome was an Rh-negative infant and for which a titre index was available, 5 had an index of over 60, and 17 had an index between 41 and 60. Most of these cases were induced, since, although it was known that the father was heterozygous, we could not be certain that the infant was negative. However, despite this we have no evidence that prematurity adversely affected in any way the small number of negative infants which resulted from this procedure. All but one of the induced Rh-negative infants survived and are now alive and well. The one neonatal death occurred from cerebral haemorrhage in a baby induced at 40 weeks' gestation.

The other complicating factor is the presence of severe oedema in the mother. In our hands a falling antibody titre may be associated with developing maternal oedema, and care must be taken in such a case not to conclude that the infant is Rh-negative. In Table I the neonatal death shown against the maternal titre of 1/128 illustrates this point. The mother was grossly oedematous and the infant at birth was hydropic and did not breathe. The titre of antibodies present in the cord-blood of this infant suggests that the maternal titre should have been 1/1,024. This case, however, is exceptional in our experience in the degree of reduction of the

maternal antiglobulin titre. In most cases of maternal oedema the indirect antiglobulin titre, if reduced at all, is affected by only one tube dilution, and more rarely by two. Appropriate care must be exercised, therefore, in determining the prognosis where pregnancy is complicated in this manner.

Evaluation of the Policy of Induction of Labour

If Rh-negative infants are excluded, there have been 194 infants resulting from spontaneous labours and 179 infants from induced labours in the present series (Table IV). The spontaneous group includes some that were left to proceed to term because of low maternal titres, some that went into spontaneous premature labour before induction could be started, and some that proceeded to term because they were not referred to us early enough for induction to be instituted. Among the induced group 61 (or 30% of the induced infants) resulted from pregnancies which were terminated before the 37th week.

The pregnancies which terminated spontaneously are notable for the large number of stillbirths, all but 4 of the total of 65 occurring in this group. Of the 61 spontaneous stillbirths, 48 resulted from pregnancies of less than 37 weeks, and 34 of these were from pregnancies of less than 35 weeks. Thus, of the remaining stillbirths, only 27 could possibly have been affected by inducing labour at the 35th or 36th week. Some of these, moreover, had been dead *in utero* for varying lengths of time before birth, so that only a proportion would have been born alive had they been successfully induced. It is possible that half of these may have been retrieved in this way.

There were 15 neonatal deaths in the spontaneous group. Seven of these infants were born to mothers with a titre of 1/1,024 or higher after 37 weeks' gestation. Most of these, perhaps five, could have been retrieved had they been induced at the 35th or 36th week.

Of the total of 76 stillbirths and neonatal deaths in the spontaneous group it is possible, therefore, that 25% could have been saved if induction had been carried out early, followed by prompt and adequate exchange-transfusion.

Among the 179 induced infants there were 19 neonatal deaths and 4 stillbirths. The 11 deaths and 2 stillbirths in the under 37 weeks group probably represent the irreducible mortality by our methods of treatment. However, perhaps four of the eight deaths in the 37 weeks and over group might have been prevented if induction had taken place one or two weeks earlier.

It is possible to make the converse calculation and estimate how the severity of the cases in the induced group would have been affected if they had all been left to go to term. There were 36 cases induced at 35 and 36 weeks for which an indirect antiglobulin index is available. If it is assumed that the titre at delivery would have persisted at the same level for another four weeks—that is, until full term—the antiglobulin index can be recalculated by using the last six weeks of the actual pregnancy and adding the remaining four weeks. When this is done, 8 of the 36 cases would have had the antiglobulin index increased by 10 or more points. Eleven of the cases would not have changed their antiglobulin index, but since 10 of these already had an index

above 60 at the time they were induced it is most unlikely that many of them would have continued to term and produced a living infant.

The above estimate is based on the assumption that no increase in the maternal antiglobulin titre would occur between the 35th and 36th weeks and full term. In actual fact, of course, many of the titres would have risen considerably, producing a more serious prognosis in an even greater proportion of cases. Further, the same arguments would apply to those induced at the 37th–38th week of pregnancy if they had been allowed to go to full term.

If these figures are used as a guide it is possible that at least another 20 neonatal deaths and stillbirths might have resulted in our series if no induction of labour had been performed. This would have meant a total foetal wastage of 119 (31.9%) in 373 cases of incompatible infants born to Rh-immunized mothers if all pregnancies had been allowed to terminate spontaneously. In contrast to this, if we had been able to apply our rules for induction and treatment in every case in our series it is likely that the number of neonatal deaths and stillbirths would have been reduced to 76 (20.4%). On this basis we can conclude that the uniform adoption of early induction of labour in cases where the antiglobulin titre of the maternal serum indicates the need, followed by prompt and adequate exchange-transfusion, would effect an overall reduction of mortality of 11%, or, put in another way, one in every three of the foetal deaths would be saved.

Discussion

The arguments for and against the early induction of labour in the treatment of haemolytic disease of the newborn have been stated many times during the past ten years. Diamond (1947) reported the use of induction of labour, but, following the demonstration by his group that kernicterus was more commonly associated with the immature infant, its use was gradually abandoned (Allen *et al.*, 1950). More recently, however, the same group has concluded that a certain number of stillbirths can undoubtedly be prevented by premature induction of labour. They recommend induction at 37 weeks, when the conditions are obstetrically favourable and the foetus is of good size and viable (Allen *et al.*, 1954; Allen, 1957).

The main argument in England against induction of labour in the treatment of haemolytic disease rests on the analysis of a series of controlled clinical trials (Mollison and Walker, 1952; Armitage and Mollison, 1953). In the analysis of these trials a critical comparison was made between the number of deaths (including stillbirths) in a group of 77 infants resulting from artificially terminated pregnancies and 108 infants from spontaneously terminated pregnancies. Although the stillbirths were reduced in the former group the neonatal deaths were increased, so that the overall mortality was 36.4% for the induced group compared with 24.1% for the spontaneous group.

The difference in mortality, as the authors were careful to point out, was not significant at the 5% level. But they go on to conclude, on the basis of the results obtained, that induction is unlikely to improve the survival rate by more than 1%.

TABLE IV.—*Outcome of Pregnancies Terminated Spontaneously or Artificially. Rh-negative Infants have been Excluded*

Length of Gestation	Maternal Indirect Antiglobulin Titre at Time of Delivery															Total
	1/128 or Lower			1/256			1/512			1/1,024 or Higher			All Titres			
	Still-births	Died	Survived	Still-births	Died	Survived	Still-births	Died	Survived	Still-births	Died	Survived	Still-births	Died	Survived	
Spontaneous:																
Under 37 weeks	1	1	1	0	1	2	2	2	0	45	3	1	48	7	4	59
37 weeks and over	1	0	61	2	1	16	1	0	19	9	7	18	13	8	114	135
All durations	2	1	62	2	2	18	3	2	19	54	10	19	61	15	118	194
Induced:																
Under 37 weeks	0	0	3	0	2	7	0	0	15	2	9	23	2	11	48	61
37 weeks and over	0	0	22	0	1	28	0	2	28	2	5	30	2	8	108	118
All durations	0	0	25	0	3	35	0	2	43	4	14	53	4	19	156	179

In assessing the results of these trials it is most important to remember that not all the infants in the trials were treated by adequate exchange-transfusion after birth. The failure to do this in all cases would certainly bias the results unfavourably against the immature infants (cf. the mortality of 13% in our own induced group, or 16% in the induced group of Fisher (1957), with the 36% for the induced group in the clinical trials).

At the time the controlled trials were carried out there was no reliable criterion which could be used to distinguish the mild, severe, or very severe case before birth. The results set out in the present paper show that such a criterion is now available. The indirect antiglobulin titre of maternal serum is a reliable prognostic tool. Further, if titrations are carried out regularly from the 26th week of gestation the values can be used to construct an antiglobulin index. The evaluation of the antiglobulin index shows conclusively that exposure of the foetus to high antibody levels continuously lessens the viability of the infant and increases the risk of stillbirth and neonatal death.

Unfortunately, few workers have achieved success in using antenatal titrations of the maternal serum as a prognostic tool. Thus Mollison (1956), though citing an earlier paper from this laboratory, records the disappointing results obtained in many other laboratories. Part of this confusion is due to the variety of techniques employed for titrating incomplete antibodies in the maternal serum, not all of which are efficient in discriminating mild from severe cases. For example, Widelock *et al.* (1956), using trypsinized cells, have demonstrated a relationship between maternal titre and foetal wastage in a series of 230 cases. But there was a 12% foetal wastage even in the titre categories of 1/8 or less. We have shown previously (Kelsall *et al.*, 1957) that the same lack of efficient discrimination holds also for titration values obtained by the plasma albumin method (Wiener *et al.*, 1952). However, even workers using the indirect antiglobulin procedure are not uniformly successful in obtaining titration results which are of value for prognostic purposes.

We have carefully studied the reasons for the discrepancies between our own results, which, as we have shown, provide an excellent prognostic tool, and those of other workers using the indirect antiglobulin technique. We are convinced that the main fault lies in the failure of most workers adequately to wash the cells used in the indirect antiglobulin titration. The need to wash the sensitized cells was stressed by Coombs *et al.* (1945) in their original description of the technique, but they warned against too much washing, because of the theoretical possibility of removing antibodies from the cells. We have now shown that this fear is groundless, so far as Rh antibodies are concerned, and that the most vigorous washing of sensitized cells is necessary in order to ensure maximum and reproducible titre end-points in Rh-antiglobulin titrations (Vos and Kirk, 1958).

In order to standardize the cell-washing procedure we have developed a mechanical cell-washing machine, which we now use in our laboratories. Laboratory workers inexperienced in antiglobulin titrations using this machine can obtain reproducible results with a minimum of training. The actual details of the indirect antiglobulin procedure used in these laboratories have been published previously (Kelsall *et al.*, 1957; Vos and Kirk, 1958).

Finally, we agree with Walker and Mollison (1957), when they point out that although exchange-transfusion is not a difficult operation the best results are obtained in hospitals where the staff treat a large number of cases and gain considerable experience.

The main points of our exchange-transfusion technique have been summarized recently (Kelsall *et al.*, 1957), and a more detailed description was given by Kelsall and Vos (1952). We have aimed at the utmost simplicity in the design of the transfusion apparatus and in most cases have used the umbilical vein route for the transfusion. The most important differences between our technique and that recom-

mended by Walker and Neligan (1955) is in the anticoagulant used and the quantity of blood transfused. Early experience with citrated bank blood, even with the addition of calcium gluconate, suggested that it placed an undue strain even on a moderately affected infant. We now use only fresh heparinized blood drawn from donors immediately before the transfusion and held at 37° C. until ready for use. Our work in this regard has been greatly facilitated by the W.A. Division of the Australian Red Cross Transfusion Service, which maintains a panel of Rh-negative donors available for immediate call. 30–40 ml. of blood is first removed from the infant and replaced with a slightly greater quantity. In this way a positive balance is built up gradually; 150–250 ml. of blood per lb. (330–550 ml. per kg.) of body weight is used, giving a total of about 1 litre per exchange. The time required for the transfusion is approximately one and a half hours.

Using this technique, we have avoided the signs of cardiac embarrassment so often associated with use of citrated blood. Even in seriously affected infants the exchange is well tolerated, and in most cases the infants sleep throughout exchange.

Despite the warnings given by other workers on the danger of overloading the circulation we have found little evidence for this in our own cases. Since July, 1954, of the 110 exchange-transfusions performed, six infants subsequently died; only one (Case 450) showed signs of circulatory collapse; two died from other causes; two survived three days after transfusion; and one (cord Hb, 4.0 g./100 ml.) was moribund when the transfusion started, and died soon afterwards.

Conclusion

The use of controlled induction of labour, followed by prompt and adequate exchange-transfusion, has a definite place in the treatment of haemolytic disease of the newborn.

The indirect antiglobulin titre of the maternal serum provides a reliable guide in the management of the Rh case.

Regular weekly or fortnightly tests of the serum of all Rh-negative mothers should be begun not later than the 26th week of pregnancy. If antibodies are present an antibody titration should be carried out.

If the indirect antiglobulin titre remains at or below 1/64 the pregnancy can be allowed to proceed to spontaneous termination, and the infant can be left untreated.

If the titre is higher than 1/128 at the time of delivery the infant should be exchange-transfused promptly. But if the titre at the time of delivery is 1/128 some discretion may be exercised. Where the cord-blood haemoglobin is high and no free Rh antibody is present in the cord serum the infant can be left untreated initially. If there is any doubt about the outcome, however, it is always better to carry out the exchange-transfusion.

The pregnancy should be terminated at the 35th–36th week if the titre at that time is 1/512 or higher. The longer the titre has been at 1/512 or higher the more urgent is the need for induction of labour and prompt exchange-transfusion. If the titre is 1/128 or 1/256 induction is indicated at the 37th–38th week. The longer the titre has been at these values the earlier the need for induction.

If these rules are applied uniformly we believe that a valuable reduction in foetal wastage due to Rh incompatibility can be achieved.

We are indebted to the medical and nursing staff of the King Edward Memorial Hospital for Women for their co-operation at all times, and to our clerical and laboratory staff for their excellent work throughout. We also thank the several hundred

patients and their supervising physicians who have placed themselves in our care during the last six years. We hope that our results will help to discharge the debt of gratitude we owe them. The Research Grants Committee of the University of Western Australia gave financial assistance which made possible the sorting and analysis of the statistical material.

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LONG-TERM ANTICOAGULANT THERAPY FOR CORONARY THROMBOSIS

BY

M. TOOHEY, M.D., M.R.C.P.

Physician, New End Hospital, London

As a result of the early promising reports (Nichol and Fassett, 1947; Owren, 1954; Tulloch and Wright, 1954) on the value of long-term anticoagulant therapy for coronary heart disease, it was decided to treat all severe cases of coronary thrombosis with continuous anticoagulant therapy. The following gives the preliminary results of this trial.

Selection of Patients

From 1955, all patients (except those who could not operate) discharged from New End Hospital who had sustained a severe attack of thrombosis or who had had recurrent episodes of infarction were kept on continuous anticoagulant treatment. Patients who had had only a moderately severe attack of thrombosis, without complications such as heart failure, or who had had only a single episode of infarction, were not treated. To date 117 patients have been under treatment for at least six months and are the subject of this report.

For purposes of comparison all patients with coronary thrombosis discharged from New End Hospital between 1948 and 1955 were followed up (Table I). Non-cardiac deaths were excluded, as were all patients who died within one month after discharge from hospital.

TABLE I.—*New End Control Series, 1948–55*

	6 Months	12 Months	18 Months	24 Months
No. followed up ..	125	125	125	125
Mortality ..	18 (14.5%)	26 (20.8%)	32 (35.6%)	39 (31.2%)

As an unusually high proportion of patients with coronary thrombosis are admitted to New End Hospital, to obviate any possibility of bias all patients with proved coronary thrombosis discharged from other hospitals in the same

group between 1953 and 1955 were also followed up (Table II). The mortality rates for both groups are statistically similar, and the two groups can therefore be regarded as one. Table III gives the combined mortality rate for both groups. In every case a copy of the death certificate was obtained to verify the cause of death.

TABLE II.—*Whittington Control Series, 1953–5*

	6 Months	12 Months	18 Months	24 Months
No. followed up ..	202	202	200	163
Mortality ..	19 (9.4%)	34 (16.8%)	47 (23.5%)	54 (33.1%)

TABLE III.—*Combined New End and Whittington Control Series*

	6 Months	12 Months	18 Months	24 Months
No. followed up ..	327	327	325	288
Mortality ..	37 (11.3%)	60 (18.3%)	79 (24.3%)	93 (32.2%)

Results of Treatment

Table IV shows the results of long-term anticoagulant therapy for 117 patients treated for six months or longer. The mortality rate for the first six months was 1.7% com-

TABLE IV.—*Long-term Anticoagulant Treated Series*

	6 Months	12 Months	18 Months	24 Months
No. followed up ..	117	99	77	42
Mortality ..	2 (1.7%)	3 (3.0%)	9 (11.6%)	9

pared with 11.3% in the untreated control series (Table III). Ninety-nine patients have been treated for 12 months or over, and for these the mortality rate at 12 months was only 3.0%, compared with 18.3% for the control group. To date, 77 patients have been treated for 18 months or longer, with a mortality rate of 11.6%, compared with 24.3% for the control series. These results are statistically significant. The number of patients treated for two years or longer is too small for any statistical analysis.

As mentioned earlier, only the more severely ill patients were treated. The untreated group of patients discharged from New End from 1955 onwards therefore consisted only of those with less severe attacks of thrombosis without complications and those sustaining their first episodes of infarction. It was therefore to be expected that the mortality rate in this group would be lower than that in the unselected control group. This proved to be so, as can be seen from Table V, which shows the mortality rate of untreated patients discharged from New End Hospital from 1955 onwards (from which date nearly all patients with severe or recurrent episodes of thrombosis were selected for long-term anticoagulant treatment). The mortality rates at 6, 12, and 18 months were 3.6%, 10.3%, and 15.1%, compared with 11.3%, 18.3%, and 24.3% for the control group.

TABLE V.—*New End Untreated Series, 1955–7*

	6 Months	12 Months	18 Months	24 Months
No. followed up ..	109	87	66	45
Mortality ..	4 (3.6%)	9 (10.3%)	10 (15.1%)	11

TABLE VI.—*Combined Anticoagulant Treated Cases and Untreated Series, 1955–7*

	6 Months	12 Months	18 Months	24 Months
No. followed up ..	226	186	143	87
Mortality ..	6 (2.6%)	12 (6.4%)	19 (13.2%)	20

Table VI shows the combined mortality rate for the 226 patients (treated and non-treated) discharged from New End from the time that nearly all severe cases were treated with anticoagulants. It can be seen that there is a significant reduction in the overall mortality rate. This mortality rate could almost certainly have been lower still if the deaths