ASSESSMENT OF SEVERITY AND MANAGEMENT OF ERYTHROBLASTOSIS FOETALIS*

by

R. N. DUTTA, M.B.B.S. (Cal.), M.R.C.P. (Edin.), Mc. Path.

and

BARBARA GHOSH, M.B.B.S. (Bom.), D.C.H. (Lond.)

When Landsteiner and Weiner (1940) discovered the RH factor, Levin *et al* (1941) showed that in 90% of the cases of erythroblastosis, the mother was RH negative. With the discovery of RH immune type of antibodies by Race (1944) and by Wiener (1944) which can cross the placental barrier, it became evident that immune types of Rh antibodies cause erythroblastosis foetalis.

If the mother has not been exposed to Rh antigen either by injection or transfusion of Rh positive blood or by a previous miscarriage, then no Rh antibodies would appear in her blood during the first pregnancy and the first infant escapes. It is in the subsequent pregnancies that Rh antibodies, immune type, appear and an antenatal check up of Rh immune antibody titre in the mother then helps in predicting the degree of of severity of erythroblastosis foetalis (Davidsohn and Stern, 1948; Mollison and Cutbush, 1949; Kelsall *et al* 1958; Freda, 1966).

Weiner *et al* (1952) stated that the mortality rate was closely correlated with the height of the titre of the maternal (albumin type) antibodies antenatally. Zeitlin and Boorman (1963) found that maternal antiglobulin titre is of value in the prediction of the disease in the baby.

Management of erythroblastosis foetalis is influenced by the (1) maternal antibody titre, (2) by obstetrical history, (3) probable Rhesus zygosity of the husband, (4) clinical picture in the newborn baby, (5) level of cord haemoglobin and serum bilirubin, (6) prematurity and any other medical complications like toxaemia, diabetes, etc. (Mollison and Walker, 1965; Freda, 1966).

The present paper presents the (1) assessment of severity of erythroblastosis foetalis based on antenatal antibody titre in Rh negative pregnant mothers and (2) management of the haemolytic disorder of the newborn due to Rh iso-immunisation of mothers.

Material and Method

Out of a total of 4,512 deliveries, 65 cases of Rh negative women were detected and studied for the incidence of Rh iso-immunisation and erythroblastosis foetalis (subject of a separate paper under publication).

Rh genotyping was carried out in

**Associate Professor of Pathology and Officer-in-Charge, Blood Transfusion Department.*

***Reader, Department of Paediatrics Armed Forces Medical College, Poona 1.*

Received for publication on 5-9-1969.

all Rh negative patients by potent anti-D, anti-C, anti-E, anti-c and anti-e sera. Their husbands, whenever available, were also Rhesus genotyped. Rhesus genotyping was carried out in tubes by the standard method (Dunsford and Bowley, 1967).

Rh antibody titration was carried out in saline and also in 30% bovine albumin using CDe/cDE cells. The indirect antiglobulin test being more sensitive was also carried out according to the standard procedure. Antibody titre, in all rhesus negative mothers and also in all mothers with past bad obstetrical histories, was checked up at 5th week, 32nd, 34th and 36th weeks of pregnancy.

Immediately after the delivery, cord blood was tested for direct antiglobulin test, serum bilirubin and haemoglobin. In case the newborn baby did not show enough evidence of haemolysis and icterus warranting active interference, a constant watch was kept on the baby for the next 72 hours by periodically checking up the haemoglobin and serum bilirubin.

Exchange transfusion, once it had been decided on, was carried out using alternate withdrawal and introduction method through a single vein, preferably using the umbilical vein whenever possible (Dutta, 1968).

Results

Out of a total of 4,512, there were 65 Rh negative pregnancies (1.44%). Of these 65 Rh negative pregnancies, 17 developed Rh iso-sensitization. Table 1 below shows these 17 cases of Rh iso-immunisation with past obstetrical histories and results of present pregnancy. Titre shown in the table is of immune antibody titre titrated in 30% bovine albumin.

Table 1 shows that there were only 4 primigravidas who showed Rh iso-immunisation but had full term normal deliveries. In one case of primigravida (Case 54) with antibody titre 1/32, the blood could only be tested few days after the delivery. Passage of foetal red cells into the maternal circulation in this case during the caesarean delivery, is responsible for the increase in the Rh anti-body titre. In all the above cases in the Table 1, the titre shown is of albumin type. Indirect antiglobulin test was also carried out, but was always found to give a higher reading than the albumin test and sometimes did not show correlation with the severity. For example, in case 37, the albumin titre was 1/32 whilst indirect antiglobulin titre was 1/256, whereas the baby had very mild jaundice and no anaemia and required no treatment. All the other 13 cases are multigravidas with past histories of Rh iso-immunisation as can be seen from Table 1. All these cases came first under our observation during their present pregnancies as shown in the table excepting Case 25 who came once before as Case 1.

Table 2 below shows the correlation between the antenatal albumin type of antibody titre and degrees of haemolytic disorder in the newborn babies born of these Rh iso-immunised mothers.

All the babies born of these 4 primigravidas did not show any evidence of haemolytic disorders. They were all full term and mature. All the 13 other cases were multigravidas

TABLE 1

Rh iso-immunised 17 cases showing past obstetrical histories and the outcome of present pregnancies

No.	Case No.	Titre	Wife	Husband	Past obstet. history	Present preg.
1	49	1/2	O.cde/cde	—	Primigravida	FTND, alive
2	10	1/4	B,cde/cde	O,CDe/cDE	Primigravida	FTND, alive
3	5	1/8	B.cde/cde	—	Multigravida	Died, Eryth. Foetalis.
4	13	1/8	B,cde/cde	—	Primigravida	FTND, alive
5	3	1/8	O.cde/cde	A, CDe/CDe	1 FTND ; 2—died after 6th day of icterus.	3rd gravida ; Died of erythroblastosis foetalis.
6	2	1/8	O,cde/cde	O,cDE/cde	1-erythroblastosis 2-FTND 3 & 4-dead ; 5-FTND, alive.	6th gravida ; stillborn.
7	1	1/16	A,cde/cde	A,CDe/CDe	1-FTND, alive 2& 3 dead, erythroblastosis.	4th gravida ; icterus, exchange transf. alive.
8	25	1/32	A,cde/cde	A,CDe/CDe	1 FTND, alive 2 & 3 dead ; 4-alive, Ex, transfusion.	5th gravida, icterus; exchange Transf. alive.
9	31	1/32	A,cde/cde	—	1 & 2 FTND 3rd-Died, erythroblastosis.	4th gravida ex. Transf. dead.
10	37	1/32	A,cde/cde	A,cDE/cde	1 FTND, 2-dead, erythroblastosis, 3-FTND.	4th gravida FTND, alive.
11	54	1/32	O.cde/cde	—	Primigravida	Caesarian, Twin, alive.
12	52	1/64	AB,cde/cde	O,CDe/CDe	1, 2, 3 & 4 died of erythroblastosis.	5th gravida icterus ; ex. transf. alive·
13	53	1/128	B,cde/cde	AB,CDe/cde	1 FTND, 2, 3, 4 & 5 died of erythroblastosis, 6th living.	7th gravida still born with hydrops.
14	62	1/128	B,cde/cde	A,CDe/cDE	1 & 2 FTND, alive, 3 & 4 still born ; 5-Kernicterus, alive mentally retarded, paralysed ; 6 & 7 FTND, post natal icterus living.	8th gravida icterus; ex. transfusion, alive.
15	64	1/128	O,cde/cde	B,CDe/CDe	1, 2, 3-developed icterus, but alive.	4th gravida icterus; ex. trans. alive.
16	22	1/256	B,cde/cde	—	1-died of erythroblastosis ; 2 & 3 deep jaundice, alive ; 4-stillbirth, 40 week.	5th gravida stillbirth (intra uterine Transf.)
17	26	1/512	A,cde/cde	—	1, 2, 3-died of erythroblastosis	4th gravida Premature delivery ; dead.

TABLE 2

Antenatal correlation of the Rh antibody titre and severity of haemolytic disorder

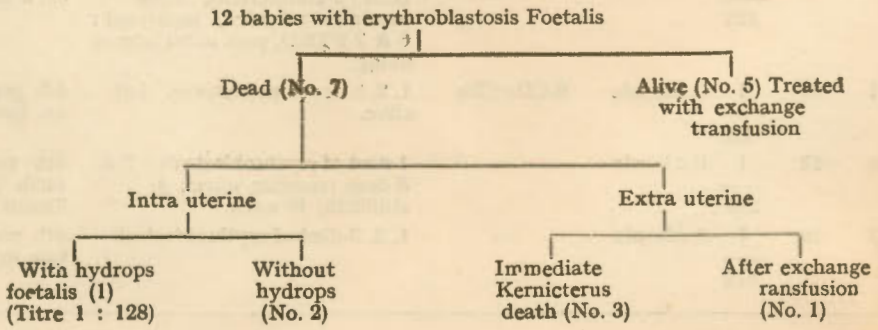
Titre of albumin antibody	Total No. of babies	Normal		Still born	Erythroblastosis	
		Primigravida	Multigravida		Dead	Alive with Trt.
1 : 2	1	1				
1 : 4	1	1				
1 : 8	4	1	—	1	2	—
1 : 16	1	—	—	—	—	1
1 : 32	4	1	1	—	1	1
1 : 64	1	—	—	—	—	1
1 : 128	3	—	—	1	—	2
1 : 256	1	—	—	1	—	—
1 : 512	1	—	—	—	1	—
Total	17	4	1	3	4	5

with past histories of iso-immunisation. In these multigravidas, an albumin titre of 1/8 or above affected the babies with varying degrees of haemolytic disorders as can be seen in Table 2 above. Only in one case of a multigravida (Case 37, Table 1) with an albumin titre of 1/32, a mildly jaundiced and anaemic son was born who required no active treatment. The mild jaundice disappeared within a very short period. All other 12 babies from 13 multigravida mothers were badly affected with erythroblastosis foetalis as can be seen in Table 3.

There were three intra uterine deaths and 4 extra uterine deaths. Mothers of these stillborn babies had antibody titres of 1/8, 1/128 and 1/256. There was one case of hydrops foetalis (titre 1/128). This case (see Table 4) was referred to us from an outstation. Already, she had lost her 2nd, 3rd, 4th and 5th babies. First and sixth are alive and both are daughters. As the husband was heterozygous and as she was keen to have a son, she was referred to us. At 30th week of pregnancy, her albumin antibody titre was already 1/128 and indirect antiglobulin titre was 1/256. It was decided to carry out a premature delivery about 34th week and then exchange the blood, but intra-uterine death occurred at

TABLE 3

Varying degrees of erythroblastosis foetalis and its outcome



31st week. Another case of intra-uterine death (Case 22) came to us during her 5th pregnancy. Her 4th child was a stillborn one and her albumin antibody titre was 1/256 at 20th week whilst the indirect anti-globulin titre was 1/512. It was decided to carry out intra-uterine transfusion which was given by an unit at Bombay with considerable experience, but the foetus did not survive. Amongst the 3 extra-uterine deaths, Case 26 was referred to us during her 4th pregnancy. Her previous obstetrical history was bad. She had already lost her 1st, 2nd and 3rd babies of kernicterus. Her antibody titre was 1/512. A premature, deeply icteric baby was delivered at 35-36th week and before any exchange transfusion could be carried out, the baby expired within few minutes of birth.

birth before any active treatment could be carried out.

Management of cases

In this series, exchange transfusion was carried out in 6 cases with one fatal result (see Table 4). The other 5 cases had an uneventful recovery. In two of them, a second exchange transfusion had to be carried out. The method followed is alternate withdrawal and introduction through a single vein, preferably the umbilical vein, as described by Dutta (1968). Criteria or guide lines adopted in these cases of exchange transfusions are:

(i) Past obstetrical history of the mother.

(ii) Antenatal immune antibody titre in the mother.

(iii) Clinical evidence of pallor, oedema, jaundice and hepatosplenomegaly.

(iv) Haemoglobin-10 gms% or less, and serum bilirubin-15 mgms% or more with a strongly positive anti-globulin test.

TABLE 4

Details of 12 cases of erythroblastosis and treatment.

Albumin antibody titre	Still born Rh + ve		Post-natal death		Alive, exchange transfusion
	No. hydrops	With hydrops	Without Trt.	After Ex. Trans.	
1 : 8	1		2		
1 : 16					1 (Case No. 1)
1 : 32				1****	1 (Case No. 25)
1 : 64					1 (Case No. 52)
1 : 128		1***			2 (Case No. 62, 64).
1 : 256	1*				
1 : 512			1**		
Total	2	1	3	1	5

* (Case 22) Tried intra-uterine transfusion.
** (Case 26) Tried premature delivery.
*** (Case 53) hydrops foetalis.
**** (Case 31) died following exchange transfusion.

There were three cases of postnatal deaths. Case 31 (see Table 4) died following exchange transfusion. The other two cases were full term normal deliveries, but died soon after

Some of the interesting cases are described below:

Case 1

This case came first under our observation during her 4th pregnancy. She gave a past history of the first baby being a full term normal delivery, whereas the 2nd and 3rd babies died of erythroblastosis within a few days of delivery. The patient's blood group was A, cde/ede whilst her husband's was A, CDe/CDe. Her albumin antibody titre at term was 1/16. She delivered a girl whose cord blood was strongly positive for direct antiglobulin test. The serum bilirubin 6 hours after birth was 16 mgm%. Her blood group was A, CDe/cde. She was treated with exchange transfusion and made an uneventful recovery.

Case 52

This case came under observation during her 5th pregnancy. She gave a past history of Rh iso-sensitization and death of 4 earlier babies. The 2nd, 3rd and 4th babies had severe jaundice and all the three died, 2nd and 4th babies within 8 hours of birth and 3rd within 3 days. Patient's blood group was AB, cde/cde whilst husband's was 0, CDe/CDe. At 32nd week, her albumin antibody titre was 1/64. She had a premature labour at 34 weeks and delivered a group B Rh positive baby with serum bilirubin of 8 mgm% and a strongly positive direct antiglobulin test. Within 6 hours of birth, the serum bilirubin went up to 18 mgm% and the level of haemoglobin dropped from the original 14 gms% to 10 gms%. The first exchange transfusion wth 280 ml fresh Rh—ve blood was carried out within 12 hours of delivery. As the serum bilirubin level went up to 30 mgm% within 48 hours of exchange transfusion, a second exchange had to be carried out. The baby recovered without complication, though a "top up" transfusion had to given prior to the discharge.

Case 62

Patient with blood group B, cde/cde, came first under our observation during her 8th pregnancy. She gave a past history of 1st and 2nd issues being full term normal deliveries, whilst 3rd and 4th were stillborn. The 5th baby was jaundiced, at birth, now 4 years old, shows spastic paraplegia with considerable mental retardation. The 6th and 7th were full term normal deliveries, both babies now alive and healthy in spite of a history of neonatal jaundice. Her husband's blood group was A, CDe/cDE. She came as an unbooked emergency case. Her antiglobulin was tested 24 hours after the birth of the baby when it developed jaundice and was 1/128. She delivered a Rh positive son whose blood tested 24 hours after birth showed strongly positive direct antiglobulin test with a serum bilirubin of 20 mgm%. Baby's weight was approximately 5 lbs. An exchange transfusion with 380 ml of group 0 Rh negative fresh blood was carried out without any complications. The baby made an uneventful recovery and was given a "Top-up" packed red cells' transfusion approximately after a month of the exchange.

Case 64

This case came during her 4th pregnancy with past history of 3 babies suffering from deep neonatal jaundice. Her blood group was 0, cde/cde whilst her husband's was B, CDe/CDe. Patient delivered a Rh positive group 0 girl who was deeply jaundiced with a strong directly positive antiglobulin test. Baby's haemoglobin was 11 gms% and serum bilirubin went up to 30 mgm% within 9 hours of birth. The first exchange through the umbilical vein was carried out within 12 hours of birth without any complications. A second exchange within the next 48 hours had to be carried out as the serum bilirubin level again went upto 26 mgm%. After the second exchange the baby made an uneventful recovery.

Discussion

Antenatal assessment of the severity of iso-immunisation was done on the basis of the maternal antibody titre (Weiner, 1954; Mollison and Cutbush, 1949). Rh antibodies for the assessment were titrated in 30% bovine albumin, though a saline titration and antiglobulin titration were also carried out.

Weiner *et al* (1952) found close correlation between the height of maternal Rh antibody titre antenatally and mortality rate due to erythroblastosis foetalis. Wiener (1952) found a mortality rate of 12.2% with an (albumin) antibody titre of 4 units or less and 72.2% rate with titre upto 256 units. We found that in multigravidas a titre of 1/8 and above can affect the babies with varying degrees of haemolytic disorders. In this series (Table 4), babies required exchange transfusion whenever the mother's antepartum albumin Rh antibody titre was 1/16 or above. A stillbirth at 1/8 titre even in an iso-immunised multigravida mother is rare, whereas, the chances become frequent with a titre of 1/128 and above (Table 2). Only Case 2 had a stillbirth with an antibody titre of 1/8, but her past obstetrical history was bad as she had two (3rd and 4th) stillbirths in earlier pregnancies. With previous histories of iso-immunisation and stillbirth, it is preferable then to perform amniocentesis and examine the amniotic fluid to have a better assessment of the severity. Freda (1966) carries out bi-weekly or weekly spectrophotometric scanning of the amniotic fluid once the "critical level" of 1/16 antiglobulin titre in her laboratory is exceeded. We have not carried out any amniocentesis in this series and have assessed the severity only on the level of the albumin Rh antibody titre.

Mollison and Walker (1952), Kelsall *et al* (1958) found that the indirect antiglobulin titre of the maternal serum provides a reliable guide in the management of cases, especially in "first affected pregnancies". Kelsall *et al* (1958) recommended termination of pregnancy at 35-36 week if indirect antiglobulin titre of the maternal serum is 1/512 or higher. If the titre is less than 1/64, then no treatment is required and if more than 1/128, then an exchange transfusion is given. Various authors, like Walker *et al* (1957), Tovey and Valaes (1959), laid down slightly different criteria of assessment and treatment. We found in our laboratory that the antiglobulin tests gives a higher reading as it is more sensitive. In this series, that in the already iso-immunised multigravida mothers with past bad obstetrical histories, the albumin Rh antibody was found to be more reliable than indirect antiglobulin test in predicting the severity and also in taking a decision on premature delivery or intra-uterine transfusion. For example, in case 37 (Table 1) the mother's albumin titre was 1/32 whilst antiglobulin titre was 1/256. On the basis of the albumin titre, we allowed the pregnancy to proceed to term when she delivered a mildly jaundiced healthy baby who required no further treatment. In already iso-immunised multigravida mothers with past histories of stillbirths in earlier pregnancies, an albumin titre of 1/64 and above is an indication for premature delivery at about 34 to 36 week and immediate exchange transfusion. With an albumin titre of 1/256 or above in an iso-immunised mother with previous histories of stillbirth, the foetus will die in utero due to anoxaemia unless an intrauterine transfusion is carried out. For this measure, a prior amniocentesis is carried out after the 24th week

of gestation and before the 30th week and a spectrophotometric scanning of the amniotic fluid is carried out. Amniocentesis, in recent years, has become an extremely important diagnostic tool in the antepartum assessment of the severity and management of such cases (Liley, 1961, Crosby and Merrill, 1965, Freda, 1966). In this series, case 22 was given an intra-uterine transfusion as her antibody titre was 1/256 at 20th week. Case 26 with an albumin Rh titre of 1/512 had a premature induction. In both these two cases, the babies could not be saved.

Various authors have laid down indications for exchange transfusion based on haemoglobin level or serum bilirubin level or both. Mollison and Walker (1952) laid more stress on cord haemoglobin in deciding exchange transfusion, an experience similar to that of Walker and Neligam (1955). Whereas, Zuelzer and Cohen (1957) laid more stress on serum bilirubin, we depended on the level of both. Whenever the haemoglobin level was 10 gms% or less, serum bilirubin 15 mgms% or more, we carried out exchange transfusion. If the cord serum bilirubin level at birth was less, as in case 52, then we watched the baby and checked up serum bilirubin and haemoglobin periodically. In case 52, the serum bilirubin rose to 18 mgm% within 6 hours of birth from its original level when exchange of blood was carried out. In the management of cases an early exchange transfusion is considered superior to simple transfusion (Mollison and Walker, 1952). Walker and Neligam (1955) calculated that 80 ml per lb (176 ml per kg) body weight should result in 85% of the baby's blood being replaced by the donor's blood. This is in accord with the recommendation of Weiner and Waxler (1946). A maximum amount of 400-500 ml was given, though Weiner *et al* (1948) suggested as much as 1000 ml in severly affected infants. Exchange transfusion was carried out through a two-way stop cock which is fitted on one end to a polythene cannula through a needle and on opposite side to a 10 ml or 20 ml glass syringe with a luer lock device. The side opening was connected to the bottle of blood. Exchange was carried out through a vein, preferably the umbilical vein, adopting an alternate withdrawal and introduction method (Dutta, 1968). Weiner *et al* (1952) deprecate this method as being a blind one which may cause damage to intra-abdominal vessels, peritoneal haemorrhage, peritonitis and splenic rupture. We did not, in this series, meet with any such complications, as has been described, but we did lose one baby (case 31) due to sudden anoxia. Weiner *et al* (1952) advocate simultaneous bleeding from radial artery and introducing blood through internal saphenous vein. They claim 100% success by this method. This method has been successfully tried in one of the local cases with a severe degree of jaundice, not due to Rh iso-immunisation and, therefore, not included in this series. We find the alternate withdrawal and introduction method is the safer and simpler of the two and hence has been used by us. However, the number of exchange transfusions carried out by us is too small to draw any firm conclusion on the merit or demerit of the two pro-

cedures.

Allen *et al* (1958) suggested a second exchange if jaundice increases in spite of a first exchange. In cases 52 and 64 of this series, a second exchange transfusion had to be carried out as the serum bilirubin, after the first exchange again went up beyond 20 mgm% within 48 hours. Our criteria for the 2nd exchange transfusion was rise of serum bilirubin to 20 mgm% and above after the first exchange. According to Mollison (1967), a second exchange is seldom necessary in mature infants, but is fairly often indicated in premature infants. Case 52 delivered a premature infant at 34 week in whom a second exchange was carried out. In two cases (52 and 62), a "top-up" packed red cell transfusion became necessary after nearly a month to booster up the low haemoglobin level.

Conclusions

Iso-immunisation of Rh negative mothers is not uncommon in India. In 65 Rh negative mothers, 17 were found to be iso-immunised.

In these iso-immunised mothers, periodical antenatal check-up of albumin type of Rh antibodies helps in the assessment of severity and management. Indirect antiglobulin test, though more sensitive than albumin type, is less reliable in the multigravida.

Babies born of multigravida iso-immunised mothers with an albumin titre of 1/8 or above antenatally will require treatment with exchange transfusion. Stillbirth is frequent with an antenatal titre of 1/64 or above. Premature delivery at 34-35 weeks of pregnancy and immediate exchange of blood may save the baby. With higher titres than 1/64 in the earlier weeks of pregnancy, intra-uterine transfusion might save the foetus from anoxaemia. Amniocentesis has, in recent years, become an important diagnostic method to assess the antepartum severity and management.

Further assessment for exchange transfusion depends on the level of haemoglobin and serum bilirubin of the cord blood and direct antiglobulin test. Exchange transfusion was carried out whenever the haemoglobin level in the new born baby was 10 gms% or less and serum bilirubin level was 15 mgm% or above, preferably with fresh blood, using the alternate withdrawal and introduction method through the umbilical vein. Sometimes, a second exchange transfusion becomes necessary when the serum bilirubin level goes up again above 20 mgm% after the first exchange.

Acknowledgement

We thank the DG AFMS for his kind permission to publish the article.

References

1. Allen, F. H. Jr., Diamond, L. K. and Vaughan, V. C.: III, Am. J. Dis. Child. **80**: 779, 1958.
2. Crosby, W. M. and Merrill, J. A.: Am. J. Obst. & Gynec. **92**: 53, 1965.
3. Davidson, I. and Stern, K.: Am. J. Clin. Path. **18**: 690, 1948.
4. Dunsford, Ivor and Bowley, C. C.: Technique in Blood Grouping, ed. 2, Edin & Lond, 1957, Oliver and Boyd.

5. Dutta, R. N.: Maharashtra Med. J. **5**: 297, 1968.
6. Freda, Vincent J.: Progress in Haematology, Edited by Brown Elmer and Moore, Carl V, Vol. V, New York and London, 1966, Grune & Stratton.
7. Kelsall, G. A., Vos, G. H. and Kirk, R. L.: Brit. Med. J. **2**: 468, 1958.
8. Landsteiner, K. and Weiner, A. S.: Proc. Soc. Exper. Biol. and Med. **43**: 223, 1940.
9. Levine, P., Burnham, L., Katzin, E. M. and Vogel, P.: Am. J. Obst. & Gynec. **42**: 925, 1941.
10. Liley, A. W.: Am. J. Obst. & Gynec. **82**: 1359, 1961.
11. Mollison, P. L.: Blood Transfusion in Clinical Medicine, ed. 4, Oxford and Edin, 1967, Blackwell.
12. Mollison, P. L. and Cutbush, Marie: Brit. Med. J. **1**: 123, 1949.
13. Mollison, P. L. and Walker, W.: Lancet. **1**: 429, 1952.
14. Race, R. R.: Nature (Lond). **153**: 771, 1944.
15. Tovey, G. H. and Valaes, T.: Lancet. **2**: 521, 1959.
16. Walker, W., Murray, S and Russell, J. K.: Lancet. **1**: 348, 1957.
17. Walker, W. and Neligan, G. A.: Brit. Med. J. **1**: 681, 1955.
18. Wiener, A. S.: R.H.—Hr Blood Types, ed. 1, New York, 1954, Grune and Stratton.
19. Wiener, A. S.: Proc. Soc. Exper. Biol. & Med. **56**: 173, 1944.
20. Wiener, A. S., Nappi, R. and Gordon, E. B.: Am. J. Obst. & Gynec. **63**: 6, 1952.
21. Wiener, A. S. and Wexler, I. B.: J. Lab. & Clin. Med. (St. Lous). **30**: 1016, 1946.
22. Wiener, A. S., Waxler, I. B. and Gamrin, E.: Am. J. Dis. Children. **68**: 317, 1944.
23. Wiener, A. S., Waxler, I. B. and Shulman, A.: Am. J. Clin. Path. **18**: 2, 1948.
24. Zeitlin, R. A. and Boorman, Kathleen, E.: J. Obst. & Gynec. Brit. Emp. **70**: 798, 1963.
25. Zuelzer, W. W. and Cohen, Flossie: Pediat. Clin. N. Am. **4**: 405, 1957.