RESULTS OF THERAPY OF ERYTHROBLASTOSIS WITH EXCHANGE TRANSFUSION

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In previous papers1, 2, 3, 4 we described the method of treatment of erythroblastosis fetalis with exchange transfusion and presented a few illustrative cases in detail. The purpose of the present paper is to summarize our results in the first 28 cases.

The rationale of the therapy of erythroblastosis by exchange transfusion can be briefly outlined as follows. According to our concept5-7 of the pathogenesis of the disease, in the typical case the Rh-positive erythroblastotic baby is born with its red cells coated with "univalent" Rh antibodies, derived from the mother during intrauterine life by transplacental filtration. In some cases, it is possible that additional Rh antibodies of the "bivalent" type (agglutinins) may be milked into the fetal circulation by the uterine contractions occurring during labor. In any event, the antibodies acting on the infant's red cells may cause them to hemolyze or to clump (by agglutination or conglutination). In cases in which only hemolysis occurs, a hemolytic anemia results which responds to simple transfusions of Rh-negative blood. If intravascular clumping takes place, on the other hand, the circulation to vital organs may become compromised producing the picture of icterus gravis, often terminating with the death of the infant with the postmortem findings of nuclear jaundice and hepatic necrosis. Obviously, such cases will not be benefited by simple transfusion since such therapy cannot reverse the process of red cell clumping. Luckily, intravascular clumping, when it occurs, probably takes place to greatest extent after birth, because in utero the conglutinin content of the fetal plasma is low.8, 9, 10 We believe that with the birth of the infant, the conglutinin content may rise to a concentration sufficient to cause clumping of the red cells. The clumping, at first, may be thought of as reversible, the red cells behaving as if they were sticky ("sludged blood," Knisely11), but in untreated cases, it is probable that the clumping eventually becomes firm, blocking the circulation. If, during the early stages of the disease the infant's blood is drained off and simultaneously replaced with type rh blood of a compatible blood group, it is likely that the disease will become aborted, because type rh blood cells cannot be clumped by the Rh antibodies in the baby's body.
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Obviously, in doing exchange transfusions the process of bleeding and infusion must be carried out simultaneously. Thus, the operation becomes progressively less efficient, because as it proceeds, more and more of the donor's blood, and less and less of the infant's blood is withdrawn, so that a complete replacement of blood is theoretically impossible. For practical reasons, it was first decided to limit the exchange to 500 cc. of blood, or about twice the infant's blood volume, and thus effectuate an 87 per cent replacement. It was subsequently found that while this was adequate in the great majority of cases, in more severe cases the remaining 13 per cent of the infant's coated red cells apparently clumped instead of lysing and thus nullified the beneficial effects of the procedure. More recently, therefore, we have modified the procedure, particularly in cases with high antibody titers, by using 1,000 cc. of blood and thus effectuating a 98 per cent replacement. In addition, as our experience has increased, other, less vital, changes have been introduced, calculated to simplify and expedite the operation. In the present paper, with but a single exception (case 10b), only those cases are presented in which 500 cc. of blood were used for the exchange transfusion. In a later paper it is intended to present a second series of cases, for comparison, in which 1,000 cc. exchange transfusions were performed.

ANTENATAL MANAGEMENT OF CASES

All pregnant women should be screened to determine if they are Rh positive or Rh negative. Grouping and Rh-Hr typing are done on the husband and all living children of those pregnant women found to be Rh negative, and information obtained as to whether the husband, if Rh positive, is homozygous or heterozygous. In certain instances, the husband's parents must be tested to obtain this important information. Since, when the maternal serum contains univalent Rh antibodies, the severity of the disease usually bears a direct relationship to the titer, the maternal serum is tested at intervals throughout the pregnancy for the presence and titer of antibodies by the saline agglutination and albumin-plasma "conglutination" technics. On the basis of information obtained from these studies, decisions can be made regarding the time of delivery of the infant and the treatment to be instituted after birth. Women who show no sensitization will, of course, be permitted to go to term because their infants will not be erythroblastotic. Mildly sensitized* women are delivered at term and the infant is treated expectantly and watched for the development of anemia, jaundice, or other signs of erythroblastosis. In those cases where moderate sensitization has developed, the infant is delivered about two weeks before term and treated with immediate exchange transfusion, using 500 cc.

* Since the same sera, in the hands of different workers, yield different values, each worker must determine for himself what values to describe as "low," "moderate," "high" and "lethal." In our laboratory, based on our experiences described in this paper, the following arbitrary limits have served as our guide: low, less than 5 units; moderate, between 5 and 20 units; high, between 20 and 50 units; lethal, above 50 units. This applies only to titers of univalent antibodies by the plasma-albumin "conglutination" method, when the saline titration shows no agglutinin to be present. As will be explained later, in the presence of agglutinins, the commonly available methods do not permit a clear-cut identification of univalent antibodies. (Cf., however, the recent paper of Wiener and Handman).
of donor's blood for the procedure. More severely sensitized women may even be delivered somewhat earlier and the infant treated by immediate exchange transfusion, using about 1,000 cc. of blood. With very high titers the fetus usually fails to survive until the period of viability, and the resultant dead fetuses are permitted to deliver spontaneously or are aborted.

**RH Typing and Antibody Tests**

The bloods of all individuals in each family were classified as to blood group and subgroup, M-N type, and Rh-Hr type. The blood grouping and M-N tests were done by the well-slide agglutination technic, while the Rh-Hr tests were done by the tube agglutination technic. The Rh antisera were obtained in part from male Rh-negative donors who had been immunized by injections of Rh-positive blood, and in part from Rh-negative mothers of erythroblastotic infants who, after sterilization, were given stimulating doses of Rh-positive blood. While the anti-Rh5 serum used was a pure agglutinating serum, the anti-rh' and the anti-rh" sera had been prepared from sera of specificity anti-Rh5 and anti-Rh6 by the addition of anti-Rh5 blocking serum. Anti-hr' serum was available from a type Rh1Rh2 woman who had had an erythroblastotic infant, and a small amount of anti-hr" serum had been kindly provided by Dr. A. E. Mourant.

The Rh antibody content of the expectant mother's serum was determined when possible at monthly intervals or more frequently according to the indications, by the saline agglutination, albumin-plasma conglutination, and at times by the blocking technic. For these titrations fresh suspensions of type Rh1, type Rh2, and type Rh cells were prepared from oxalated group O blood which had been freshly drawn from the vein, or stored no longer than seventy-two hours in the refrigerator. All suspensions were washed once by centrifuging, decanting the supernatant, and resuspending the cells in fresh saline to produce a 4 per cent suspension in terms of blood sediment. As mentioned in previous papers, the most common error in the titration technic is in preparing the serum dilutions. Improper rinsing results in 'carrying over,' and accounts for the extraordinarily high titers sometimes reported in the literature. The proper precautions to be followed have been described in previous papers and will not be repeated here. The individual titration technics were carried out as follows:

**Agglutination method.** One drop each of progressively doubled dilutions of the maternal serum was transferred to a series of small test tubes (8 mm. diameter) and to each tube was then added a drop of the test blood suspension. The mixtures were shaken and the rack was placed in the water bath or incubator at 37 C. for one hour. The tubes were then gently tilted one by one in order to dislodge the sediment, and the reactions were read under the low power of the microscope by placing the entire tube on the stage under the objective.

**Albumin-plasma conglutination method.** A duplicate titration was set up as described for the agglutination method. After the one hour incubation period when the cells had completely sedimented, the supernatant fluid was removed as completely as possible with a fine capillary pipet proceeding from the highest serum dilution to the most concentrated. Then to each tube was added a large drop of fresh albumin-plasma mixture, prepared by mixing 4 parts of pooled oxalated plasma from Rh-positive individuals with 1 part of 15 per cent human albumin or 30 per cent bovine albumin solution. The tubes were then vigorously shaken to resuspend the cells and were reincubated for another hour at body temperature. At the end of this time the tubes were individually shaken, somewhat more vigorously than for the agglutination technic, and the reactions read under the low power of the microscope.

**Blocking technic.** If the agglutination test was negative and the conglutination showed a significantly high titer, tests were usually carried out by the blocking technic. Again the first step was the titration by the saline agglutination method. Then to each tube was added one drop of an anti-Rh5 agglutinating serum diluted with saline so as to have a titer of about 10 to 20 units. The mixtures were reincubated for one hour at 37 C. and then the tubes were gently shaken, one by one, and the reactions read under the microscope.

* By removing the lower half of the ordinary low power objective one is left with a weaker objective which gives lower magnification and ample working space into which to place the test tube.
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Interpretation. For the sake of uniformity all readings were taken by the senior author. If he was not in the laboratory when the incubation period was over the racks were placed on the laboratory table at room temperature until his arrival, but this did not seem to affect the results materially. During his absence from the laboratory his assistant read the reactions. The reactions were graded as ++++, ++, +, ±, tr, and --, where +++ represents one large clump of cells, while ++ and +, etc., progressively weaker reactions, and -- represents a uniform suspension with no clumps. In the agglutination and conglutination titrations the titer (in units) was taken as the reciprocal of the highest dilution giving a one plus reaction. In the blocking test, the titer was taken as the reciprocal of the highest dilution causing complete or almost complete inhibition of agglutination. It was found that the freshness of the test cell suspensions had a more striking effect on the titers obtained than did the Rh type or the zygosity. For example, with fresh cells the conglutination titer was usually 20 to 40 times as high as the blocking titer; however, if the cells were old the conglutination titer would be lower and the blocking titer higher so that this pitfall could be recognized by a reduction in the ratio. When such abnormal results were obtained the tests were repeated with fresh cell suspensions and in this way mistakes were often avoided. The serologic titration method is crude as compared with chemical titrations and has a large intrinsic error. By performing the titrations with two different Rh-positive cells (type Rh1Rh and Rh2Rh2 as a rule) and averaging the results, this error was minimized. The titer values listed in our tables thus represent the average of at least two, and usually more titrations.

Even with these precautions the results can be considered to have an intrinsic error of about one tube, and this fact must be kept in mind when evaluating the significance of apparent titer fluctuations in tests done serially on any given patient’s serum. For example, suppose it is desired to determine if the following series of titers shows any significant fluctuation: 17, 33, 40, 19, 36 and 50. The average of these six values is 33 units. A serum that actually has a titer of 33 units could, in tests made at different times, give titer values ranging from 16 to 66 units due to variations of technic without indicating that there has been any actual fluctuation in the degree of sensitization. On the other hand, had the following values been obtained: 17, 33, 40, 19, 96, 80, 120 then one could assume that there had been a true rise in titer after the fourth sample was tested and that this rise was maintained during the last three tests. In any case of doubt the patient was recalled for another titration.

TECHNIC OF EXCHANGE TRANSFUSION*

The exchange transfusion is carried out immediately after birth, using blood from a compatible, nonsensitized type rh donor. No time is wasted in carrying out conglutination or other serological tests, hemoglobin determinations, erythroblast counts, etc., although blood is taken for these studies. In the event, however, that the father is heterozygous the baby is tested in order to be certain that he or she is Rh positive before proceeding. In certain instances it is possible to predict from the groups of the parents what group of blood will be compatible with the infant’s blood.4 In such cases, the blood can be made available before the baby is born. Where this is not possible, nonsensitized type rh donors belonging to groups A, B, AB and O are kept standing by until the infant’s blood group is determined.

The infant is immobilized on a circumcision board, and a 20 gage cannula inserted into the saphenous vein at the ankle. The infusion of blood is started after the injection of 0.2 cc. (200 units) of heparin intravenously. A three-way stopcock connects the tubing of the infusion to the cannula and makes it possible to inject medication as needed and to control the speed of the infusion. A period of fifteen minutes is permitted to elapse before the bleeding is started. This wait is important because it allows time for the heparin to exert its maximum effect and at the same

* A motion picture demonstrating our technic of exchange transfusion is available to medical societies for loan, upon application to the authors.
time permits about 50 cc. of blood to enter the infant's circulation and produce enough of plethora to make the arteriotomy an easy procedure. The radial artery is exposed through an incision made just above the lower end of the radius; it is cleaned of all adventitial tissue and lifted up on a hemostat, and with a small scalpel a flap is cut into the artery by inserting the blade into the center of the artery and drawing it diagonally outward. The flow of blood is immediate and copious. The blood is collected in one ounce medicine glasses which are emptied into a graduated bottle. The inflow and outflow of blood are measured carefully and the infusion is kept running about 50 cc. ahead of the bleeding at all times. This is easily accomplished by using a syringe on the three-way stopcock to inject the blood at an increased rate when necessary. When 250 cc. of blood have run in, a second dose of heparin is given intravenously. No further heparin injections are given, so that by the time the procedure is completed the heparin effect is nullified.

When an 1,000 cc. exchange transfusion is performed the final dose of heparin is given after 500 cc. of blood has been injected. A 10 cc. syringe containing a 10 per cent calcium gluconate solution is kept on hand at all times during the procedure, and if signs or symptoms of hypocalcemia supervene, 5 cc. are injected directly through the cannula. As a rule, no calcium is required for transfusions of 500 cc. or less, provided the transfusion is not given too rapidly, that is, within less than an hour. For larger exchange transfusions, it is best to inject 5 cc. of calcium gluconate prophylactically at the 500 cc. mark, even though the patient exhibits no untoward symptoms. In 500 cc. exchange transfusions the amount of blood injected should exceed the amount withdrawn by about 50 cc.; in the 1000 cc. transfusions a margin of about 75 cc. should be allowed. In infants severely anemic at birth this margin should be increased by another 50 cc. At the close of the procedure the radial artery is usually tied off before closing the incision at the wrist, but a snug bandage will control any venous oozing from the incision at the ankle. A small amount of sulfadiazine powder is placed into the wounds before closing them, and the infant is routinely given 20,000 units of penicillin intramuscularly every three hours for twenty-four hours after the operation. Subsequent treatment of the infant is routine, except that breast feeding is interdicted.

**RESULTS**

For the purpose of evaluating the efficacy of the treatment, the cases have been divided into four categories as follows:

1. Severe cases, with recovery
2. Fatal cases
3. Cases of moderate severity
4. Mild cases

**Severe Cases, with Recovery**

**Case 1.**—This case has been presented in detail elsewhere, and to conserve space will not be repeated here. It is, however, included in the discussion at the end of this paper.

**Case 2.**—This patient was referred to us twenty-four hours after birth. He was the product of the second pregnancy, the first and only previous pregnancy having been normal. The mother had never received any blood transfusions. The infant was jaundiced at birth and the splenic edge was palpable 3 fingerbreadths below the costal margin. After several hours, an anemia of 8.8 grams per cent of hemoglobin was found with a red blood count of 3.71 million red blood cells per cu. mm. The uncorrected
white blood count was 64,000 cells and there were 196 normoblasts per 100 white blood cells on the
smear. Anisocytosis and poikilocytosis were present to a marked degree.

Findings. Grouping and Rh-Hr tests done on the family are shown in table 1.

Antibody studies done on the mother's plasma by the agglutination technic showed the presence of
Rh antibodies of a titer of 20 units, while the titer of the Rh antibodies was 30 units by the plasma
conglutination test and 70 units by the albumin-plasma conglutination technic.* The conglutination
test for coating of the infant's red cells by univalent antibodies was positive.

Prognosis. The findings in this case pointed to a serious prognosis; namely, the high titer of Rh anti-
bodies in the maternal serum, the infant's deep jaundice, severe anemia, unusually high erythroblastemia,
as well as its poor clinical condition.

Procedure. At the start of the exchange transfusion the infant appeared to be in a condition bordering
on shock. A subconjunctival hemorrhage was present in the left eye, and small petechiae had appeared
on the forehead. The skin had a mottled appearance and there were occasional nystagmoid movements
of the eyes. The exchange transfusion was performed using blood from a donor who belonged to type
OMNrh. In order to reduce the conglutinin content, the donor's blood was first treated by removing half
of the plasma and replacing it with normal saline solution. Of this mixture, 60 cc. were injected while
500 cc. of blood were simultaneously withdrawn.

### Table 1

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group and M-N type</th>
<th>Rh-Hr type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>B N</td>
<td>Rh1 Rh1</td>
</tr>
<tr>
<td>Mother</td>
<td>O MN</td>
<td>rh</td>
</tr>
<tr>
<td>1st son</td>
<td>O MN</td>
<td>Rh1 rh</td>
</tr>
<tr>
<td>Patient</td>
<td>O MN</td>
<td>Rh1 rh</td>
</tr>
</tbody>
</table>

* The M-N tests are not clinically important but are included for the sake of completeness.

Results. The immediate response was most dramatic. The infant appeared to be more vigorous and
although there was no change in the jaundice, the color and circulation were definitely improved. The
hemoglobin on the day following the transfusion was 11.7 grams per cent and then rose to 13.2 grams.
Jaundice became intense by the fifth day, at which time the icterus index had risen to 120 units. During
this time the baby was irritable and took his feeding poorly. By the sixth day, marked clinical improve-
ment was noted. The jaundice began to fade, the petechiae noted on the forehead had been completely
absorbed, and from that time onward the baby acted well. The hemoglobin concentration continued to
decrease over a period of a month when it reached a concentration of 6.6 grams per cent, with a red blood
count of 1.5 million per mm. By this time the icterus had faded completely. The infant was given a
transfusion of 70 cc. of O, rh blood on the following day and the hemoglobin concentration rose to 9.2
grams. This child has been followed carefully for more than a year. Both his physical and mental progress
had shown no deviation from the normal. He sat at five months and stood at 11 months. At one year he
was beginning to take his first steps. His first four teeth have a greenish discoloration.

Case 3.—This patient had had five miscarriages at 3 to 5 months over a period of three years. Her
sixth pregnancy yielded a full-term infant who is normal and well. This child showed no jaundice or
anemia during her neonatal period. When first seen by us the mother was in the 33rd week of her seventh
pregnancy and had been found to be Rh negative.

Findings. Groupings and Rh-Hr tests done on the family are shown in table 2.

Antibody tests for Rh sensitization done on the mother's serum at this time showed agglutinins to be
present in a titer of 7 units, while the titer was 16 units by the plasma conglutination technic. One month

* The figures for antibody titers given in this paper represent averages of the results of at least two
titrations.13,14
later, the agglutinin titer was still 7 units, while the titer by the plasma conglutination technic was 10 units. (This difference is not significant because it is within the limits of accuracy of the method of titration).

**Prognosis.** This woman, then, was moderately sensitized to the Rh factor, and since the husband was most likely homozygous for Rh0, an Rh1rh or Rh2rh infant could be expected who would have erythroblastosis in a severe form, and might even be stillborn if carried to term.

**Procedure.** Labor was induced in the thirty-eighth week of the pregnancy. Plans had been made to do an exchange transfusion immediately after birth, but the baby was born in a city many miles away and nine hours elapsed before we arrived at the hospital. In the meantime, the infant had been found to have a hemoglobin of only 9.7 grams per cent, and there were 12 normoblasts per 100 white blood cells on the smear. The baby was given a transfusion of packed red cells from 100 cc. of O, rh bank blood. Shortly thereafter, the infant became cyanotic and was placed in an incubator. Moderate jaundice as well as cyanosis and difficulty in respiration were present when we saw the child. A few rales were present, scattered throughout both lung fields, which were interpreted as due to areas of atelectasis. Although the transfusion had raised the hemoglobin concentration to 13.6 grams, an exchange transfusion was carried out with the administration of 560 cc. of blood (half of the plasma in this blood was replaced by saline solution) and the simultaneous removal of 600 cc. of blood. During the procedure the infant required repeated aspiration of mucus and inhalation of oxygen because of several episodes of cyanosis. In tests carried out later, the cord blood of the baby typed as OMrh2, and the icterus index was 40 units.

### Table 2

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group and subgroup</th>
<th>M-N type</th>
<th>Rh-Hr type</th>
<th>Phenotype</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>O</td>
<td>M</td>
<td>Rh1rh</td>
<td>Rh1R1 or Rh1R2</td>
<td>rR or rR2</td>
</tr>
<tr>
<td>Mother</td>
<td>O</td>
<td>M</td>
<td>rh</td>
<td>r</td>
<td>r</td>
</tr>
<tr>
<td>Daughter</td>
<td>O</td>
<td>M</td>
<td>Rh1rh</td>
<td>Rh1R1</td>
<td>r</td>
</tr>
</tbody>
</table>

**Results.** Differential agglutination studies showed that the combined procedures had left only 2 per cent of the infant's own blood cells in its circulation. The hemoglobin concentration of the blood was 11.6 grams per cent on the day following the transfusion and the child was clinically very much improved. The infant remained well, but the hemoglobin concentration fell gradually and on the fourteenth day of life another transfusion of 75 cc. of Rh-negative blood was given. From this point on the baby did very well. This child has been followed with great care for about a year and has been unusually healthy as well as having showed rather precocious advancement from the developmental point of view.

**Case 4.—** This case has already been reported in detail elsewhere.4

**Case 5.—** The mother of this patient was first seen by us in the twelfth week of her third pregnancy. Her first pregnancy terminated with the birth of a normal female who is well. Her second pregnancy was attended by a midwife; labor lasted two days and yielded an apparently normal infant who was jaundiced for a few days and then seemed to recover. This baby was nursed for several days during the neonatal period. At the age of seven months the child was unable to hold up its head, had athetoid movements, followed light poorly, and had a vacuous expression.

**Findings.** Grouping and Rh-Hr tests done on the father, mother and both children are shown in table 3.

Antibody studies done on the mother's serum at intervals during her pregnancy are given in table 4.

At the time of the last test, titrations for alpha and beta antibodies were done since a possibility of double sensitization (to A as well as to Rh) existed. By the agglutination technic the anti-A titer was 48 units, while the Anti-B titer was also 48 units. With the albumin-plasma method, the anti-A titer was 160 units and the anti-B titer was 48 units.

* Using test cells of subgroup A2.
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Prognosis. On the basis of these findings there appeared to be little doubt that the expected infant would be severely affected by the disease and might even be stillborn if the pregnancy were allowed to go to term. In addition to the harm that would be done by the univalent Rh antibodies, one might expect some injury to be caused by the alpha antibodies that were present, if the baby proved to be group A.

Procedure. Delivery was spontaneous at term. The infant appeared normal at birth and had a hemoglobin concentration of 15.5 grams per cent. The erythrocytes typed as A2MN Rh, and were shown by the conglutination technic to be coated with univalent antibodies. Immediate exchange transfusion was carried out using blood from a group A, type Rh donor from which one-half of the plasma had been removed and replaced with saline. Over a period of 90 minutes 500 cc. of blood were administered and 450 cc. removed.

Results. The infant withstood the procedure well. The hemoglobin concentration of the blood after the transfusion was 16 grams per cent. However, by the seventh day it had fallen to 13.5 grams per cent and the patient became severely jaundiced. On the eighth day of life the serum bilirubin concentration was 16 mg. per cent, but this fell to normal by the fifteenth day. During this time there was a gradual decline in the hemoglobin concentration of the blood to 8.5 grams per cent, and the baby was given another transfusion, this time of Orh blood, on the fifteenth day, following which the hemoglobin concentration rose to 15.5 grams. Except for a bout of diarrhea that developed at the age of one month the baby has since done well.

This case is instructive in illustrating the method of determining genotypes. The father belonged to phenotype Rh, so that on this basis he belonged to one of the three genotypes, Rh, Rh', or Rh Rh' of which the first is the most common and therefore the most likely. For this reason, type Rh, individuals are usually presumed to be heterozygous. However, when it was found that the first two children belonged to type Rh, this excluded genotype Rh leaving genotypes Rh Rh' and Rh Rh' as the remaining possibilities. When finally the new baby proved to be Rh, it was apparent that the genotype of the father is Rh Rh so that he is homozygous for the Rh factor even though he belongs to phenotype Rh, Rh. Obviously, every future child of this couple will be erythroblastotic.
This case is unusual in that the baby developed a hemolytic anemia despite the exchange transfusion and required a supplementary transfusion before the blood count was stabilized. It is possible that this was due to sensitization with the A factor; and this interpretation is supported by the excellent response to subsequent transfusion of group O, type rh blood.

Despite the additional complication of diarrhea, the child did well, is one year old at the time of this writing and is normal.

Case 6.—This baby was referred to us at the age of 1 day for treatment by exchange transfusion. Studies done elsewhere had shown the mother to be Rh negative and the father to be Rh positive. Blocking antibodies were detected in the mother's serum during her pregnancy and were said to be '4-plus.' The baby was the result of the second pregnancy. The first baby was jaundiced at birth, but the jaundice cleared after several days without treatment, and this child is well. One and one-half years before the onset of the first pregnancy the mother had received a transfusion of blood from her husband.

Findings. On examination the infant was pale and jaundiced. The hemoglobin concentration of the blood was 11.4 grams. The spleen and liver were moderately enlarged and the child's general condition was good.

Grouping and Rh-Hr tests done on the father, mother and the infant are shown in table 5.

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group and subgroup</th>
<th>M-N type</th>
<th>Rh-Hr type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>O</td>
<td>N</td>
<td>Rh1Rh1</td>
</tr>
<tr>
<td>Mother</td>
<td>A₁</td>
<td>M</td>
<td>rh</td>
</tr>
<tr>
<td>Infant</td>
<td>O</td>
<td>MN</td>
<td>Rh₁Rh₂</td>
</tr>
</tbody>
</table>

Table 5

No antibodies could be detected by the saline agglutination test in the mother's serum, but the blocking test was positive to a titer of 16 units. By the albumin-plasma technic, univalent Rh antibodies were demonstrable in a titer of 40 units. Furthermore, the infant's cells were completely coated* by univalent Rh antibodies as shown by the fact that they behaved in the tests as though they belonged to type rh'. In addition, free univalent antibodies were demonstrated in the baby's serum in a titer of 3 units by the albumin-plasma conglutination test.

Prognosis. This infant was already erythroblastic when seen, and in view of the complete coating of the erythrocytes by univalent antibodies was probably in imminent danger of developing serious intravascular clumping.

Procedure. Exchange transfusion was performed, using the blood of a donor belonging to group O, type rh. One-half of the donor's plasma was removed and replaced with normal saline in order to reduce the conglutinin content of the infused blood. Five hundred and fifty cc. were administered into the saphenous vein and 500 cc. of blood were withdrawn from the radial artery. The baby was returned to the ward in excellent condition.

Results. The day following the procedure the hemoglobin concentration of the blood was 12 grams per cent, and the infant's general condition was good. The icterus index, which had been 60 units at the onset of the procedure, was now 64 units, and differential agglutination tests showed that a replacement of about 85 per cent of the red cells had been accomplished.

Two days after the transfusion the baby began to show signs of irritability and his temperature rose to

* The cells of all typical erythroblastic babies are coated by univalent antibodies as can be demonstrated by suspending the cells in plasma or albumin-plasma mixture, or by the anti-globulin technic. If, in addition, the baby's Rh-positive cells are "blocked," as shown by their failure to clump in good anti-Rh agglutinating serum, they are considered to be "completely coated."
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The urine was found to contain 10-15 white blood cells per high power field and culture was positive for staphylococcus aureus. The Chvostek, peroneal, and Trousseau signs were positive and the serum calcium was found to be only 7.3 mg. per cent. The child was treated with intravenous calcium gluconate, calcium by mouth and given penicillin and sulfa therapy. Within a few days the temperature fell to normal, the calcium concentration of the serum returned to normal levels and the urine cleared. When discharged at the end of eight days, the child’s hemoglobin concentration of the blood was 10.6 grams and he was clinically well. At the age of 3 months, the child weighed 15 pounds and the hemoglobin concentration was 12.2 grams per cent. There were no subsequent transfusions given, and the child developed normally.

CASE 7—The mother of this infant was first seen in the eleventh week of her fourth pregnancy. Her first and second pregnancies had ended at term, and both of these children are alive and well. Her third pregnancy resulted in the birth of a full term infant who seemed to be well at first, but then became jaundiced and was transfused eight hours after birth. This infant died on the third day of life. The clinical diagnosis made at that time was cerebral hemorrhage.

Findings. Grouping and Rh-Hr tests done on the father, mother and both surviving daughters gave the results shown in table 6. Antibody studies done on the mother’s blood at intervals during her pregnancy gave the results shown in table 7.

Prognosis. An autopsy report on the infant that died is not available, but from the clinical symptoms described it is evident that the death may have been due to erythroblastosis. This belief is strengthened by the finding of a moderately high antibody titer in the maternal serum early in the following pregnancy. Since the father was Rh positive, and almost surely homozygous, it was anticipated that the new baby would be Rh positive and also have moderately severe erythroblastosis.

Procedure. In order to limit the period of time over which the infant would be exposed to the action of the maternal antibodies, labor was induced two weeks before term. The infant, a girl, appeared to be normal. There was a faint yellow streak along the umbilical cord, but the amniotic fluid was not yellow and the vernix was not discolored. Exchange transfusion was carried out immediately using 540 cc. of blood from an A1Nrh donor for the infusion while 480 cc. of blood was withdrawn. Half of the plasma had been removed from the donor’s blood and replaced with saline in order to reduce the conglutinin content of the infused blood. The baby withstood the procedure well.

### Table 6

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group and subgroup</th>
<th>M-N type</th>
<th>Rh-Hr type</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>O</td>
<td>M</td>
<td>Rh, Rh</td>
<td>R’R’ or R’r’</td>
</tr>
<tr>
<td>Mother</td>
<td>A1</td>
<td>M</td>
<td>rh</td>
<td>rr</td>
</tr>
<tr>
<td>1st daughter</td>
<td>O</td>
<td>M</td>
<td>Rh, rh</td>
<td>R’r</td>
</tr>
<tr>
<td>2nd daughter</td>
<td>A1</td>
<td>M</td>
<td>Rh, rh</td>
<td>R’r</td>
</tr>
</tbody>
</table>

### Table 7

<table>
<thead>
<tr>
<th>Week of pregnancy</th>
<th>Titer by agglutination technic (units)</th>
<th>Titer by plasma technic (units)</th>
<th>Titer by albumin-plasma technic (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11th week</td>
<td>0</td>
<td>15</td>
<td>—</td>
</tr>
<tr>
<td>20th week</td>
<td>0</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>32nd week</td>
<td>0</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>38th week</td>
<td>0</td>
<td>11</td>
<td>30</td>
</tr>
</tbody>
</table>
Results. The infant's course was entirely uneventful except for the appearance of moderate jaundice on the second day. This subsided rapidly. No hepatic or splenic enlargement was made out at any time. The infant's blood group was A,M,Rh, and a positive reaction was obtained with the conglutination test for coating of the infant's red cells. Furthermore, free Rh antibodies of 4 units titer could be demonstrated in the baby's serum by the conglutination method. On the day following the transfusion the hemoglobin was 17.4 grams per cent and the red blood cell count 5.04 million per cu. mm. Three normoblasts per 100 white blood cells were present on the smear. The child left the hospital on the fifth day of life in excellent condition. When seen again at the age of 4 months the child was alert and head its head up well.

Case 8.—This baby, a female, was first seen on the second day of life. No antenatal studies had been done on the mother during pregnancy. Her first child was born two years previously and was well. The mother had received no transfusions or blood injections at any time. At birth the infant appeared to be normal, but on the second day of life rapidly became jaundiced. The hemoglobin concentration was found to be 11.7 grams per cent and the red blood count 2.9 million per cu. mm. Seven nucleated red blood cells per 100 white blood cells were found on the smear.

Findings. Grouping and Rh-Hr tests done on the father, mother, and infant gave the results shown in table 8.

Weak agglutinins were demonstrable in a titer of 8 units in the mother's serum, but by the albumin-plasma conglutination technic univalent antibodies were demonstrable in a titer of 40 units.

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group and subgroup</th>
<th>M-N type</th>
<th>Rh-Hr type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>A</td>
<td>M</td>
<td>Rh&lt;sup&gt;r&lt;/sup&gt;&lt;sub&gt;+&lt;/sub&gt;h&lt;sup&gt;-&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mother</td>
<td>A&lt;sub&gt;1&lt;/sub&gt;</td>
<td>MN</td>
<td>rh</td>
</tr>
<tr>
<td>Patient</td>
<td>O</td>
<td>M</td>
<td>Rh&lt;sup&gt;-&lt;/sup&gt;&lt;sub&gt;b&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

Prognosis. Inasmuch as the above titers were determined only one day postpartum, these titers were presumably the same as those existing just before delivery, so that moderately severe sensitization was present and the prognosis was fair if intravascular clumping had not already occurred, and provided that an exchange transfusion were done immediately. With simple transfusion therapy the likelihood of recovery seemed to be remote.

Procedure. Exchange transfusion was performed when the baby was 36 hours old. Over a period of one hour 550 cc. of group O, type rh blood were injected and 475 cc. of blood removed.

Results. The hemoglobin concentration of the blood was 15.9 grams per cent after the transfusion with a red blood count of 5.2 million per cu. mm. There were 4 nucleated red blood cells per 100 white blood cells on the smear. The icterus index before the procedure was 70 units and after the procedure had been reduced to 50 units. Titration of free Rh antibodies by the albumin-plasma conglutination method done on the infant's plasma showed a pretransfusion concentration of 14 units and a post-transfusion concentration of 14 units.

The baby withstood the procedure very well and the jaundice had almost completely faded three days after treatment, at which time the baby was discharged from the hospital. When seen at the age of five weeks, the hemoglobin concentration was 14.3 grams per cent and the red blood cell count was 5.05 million per cu. mm.; the baby was entirely well clinically.

The obstetrician was so impressed by the improvement of the baby by the transfusion that he sent her home with her mother on the fourth day postpartum without even consulting us. This spectacular result cannot be duplicated by any case seen in the days before exchange transfusion. Comparable cases in the past have
12. **ERYTHROBLASTOSIS AND EXCHANGE TRANSFUSION**

either showed progressive jaundice despite transfusion, with early death from kernicterus, or have recovered following a series of transfusions over a period of weeks or months, sometimes only to exhibit sequelae of liver and brain damage later on.

Case 9.—When first seen, the mother of this patient was in the interval between her first and second pregnancy. Her first pregnancy, three months previously, had been terminated by cesarean section in the thirty-fifth week because of central placenta previa. She received two transfusions at that time. The infant weighed 2½ pounds and lived for only twelve hours. Studies were requested to determine if isoimmunization had any bearing on the loss of the infant.

**Findings.** Grouping and Rh-Hr tests done on the husband and wife gave the results shown in table 9.

At the time that these studies were done, tests for antibodies in the mother’s serum showed an agglutinin titer of 2 units, while the titer by the plasma conglutination test was also 2 units. It seemed much less likely that the sensitization had been caused by the pregnancy than by the two transfusions that the woman had received. Inasmuch as the husband was most probably heterozygous for the Rh factor there

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group and subgroup</th>
<th>M-N type</th>
<th>Rh-Hr type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Husband</td>
<td>A1</td>
<td>M</td>
<td>Rh_Hr</td>
</tr>
<tr>
<td>Wife</td>
<td>A1</td>
<td>M</td>
<td>rH_Rh</td>
</tr>
</tbody>
</table>

**Table 9**

was an even chance that any future pregnancy would produce either an Rh-positive or an Rh-negative infant. Furthermore, since sensitization was only mild there was a possibility that even if she had an Rh-positive infant it would be only moderately or mildly affected and could be saved by the proper treatment.

The mother returned fourteen months later for further studies, in the twenty-fourth week of her second pregnancy, and her serum was tested for antibodies at frequent intervals thereafter with the results shown in table 10.

**Prognosis.** The absence of antibodies at the first examination, followed by their appearance at the second examination, indicated that the mother was carrying an Rh-positive fetus, and that a moderately affected erythroblastotic infant could be expected.

**Procedure.** Because of the previous cesarean section, it was felt that this child should also be delivered transabdominally. In order to limit the period of time that the infant would be in contact with the maternal antibodies, cesarean section was done at thirty-seven weeks. Before proceeding with the exchange transfusion, however, the baby’s blood was grouped and Rh tested in order to be certain that we were not dealing with an Rh-negative child. As expected from the antibody tests, the baby was Rh positive (A,MR,rh).

Exchange transfusion was performed using blood from an A,MNhrh donor. Over a period of ninety minutes, 550 cc. were given and 500 cc. removed. The baby bore the procedure well.

Table 10

<table>
<thead>
<tr>
<th>Week of pregnancy</th>
<th>Titer by agglutination technic</th>
<th>Titer by albumin-plasma technic</th>
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<td>6</td>
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<tr>
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<td>15</td>
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<tr>
<td>37th week</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>
Results. The hemoglobin concentration at birth was 17.4 grams per cent, and the red blood count 6 million per cu. mm. There was only 1 normoblast per 100 white blood cells on the smear. The icterus index was 1. The hemoglobin concentration following the procedure was 13.1 grams per cent and the red blood count 4.8 million per cu. mm. The albumin-plasma conglutination test on the cord serum could detect no free Rh antibodies, but by the acacia method a titer of 48 units was obtained on the baby's serum.*

On the day following the transfusion, jaundice appeared, and deepened perceptibly on the second day.† The icterus index at this time had risen to 72 units. The infant remained clinically well, however, and took its feedings without difficulty. The hemoglobin concentration remained unchanged. The spleen became slightly enlarged, but the liver was not palpable. By the eighth day the spleen was no longer palpable and the jaundice was fading rapidly. The patient was discharged from the hospital at the age of 2 weeks. At the age of 2 month the hemoglobin concentration had fallen to 8.4 grams, but reticulocytes were present on the blood smear and a differential agglutination test showed that as much as 90% of the infant's blood was Rh positive, indicating that regeneration of blood was proceeding at a satisfactory rate, and that further transfusion was not necessary.

When seen again at the age of 3 months, the child was perfectly well and developing normally both mentally and physically.

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group</th>
<th>M-N type</th>
<th>Rh-Hr type</th>
<th>Phenotype</th>
<th>Genotype</th>
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<td>MN</td>
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<td>R1R1 or R1r</td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>O</td>
<td>M</td>
<td>rh</td>
<td>r or rr</td>
<td></td>
</tr>
<tr>
<td>1st son</td>
<td>O</td>
<td>M</td>
<td>Rh1 Rh</td>
<td>R1r</td>
<td></td>
</tr>
<tr>
<td>2nd son</td>
<td>O</td>
<td>MN</td>
<td>Rh1 rh</td>
<td>R1r</td>
<td></td>
</tr>
</tbody>
</table>

Table 11

Fatal Cases

Case 102.—The mother of this patient was first seen in the second trimester of her fifth pregnancy. Her first two pregnancies had yielded normal infants who are well today. Her third pregnancy resulted in the birth of a stillborn fetus at term. Life had been felt until three days before delivery. Her fourth pregnancy terminated spontaneously at 36 weeks with the birth of a stillborn infant which had apparently been dead in utero for about two weeks.

Findings. Grouping and Rh-Hr tests done on the entire family gave the results shown in table 11.

Antibody tests done on the mother's plasma during the second trimester were positive to a titer of 4 units both in saline and plasma media, indicating a mild sensitization to the Rh factor, with antibodies predominately of the bivalent type. At the beginning of the third trimester, however, the antibody titer had risen to 12 units by the agglutination method and to 25 units by the plasma conglutination technic.

Prognosis. Since the husband was presumably homozygous for the Rh factor there was little doubt that the stillborn infants from the third and fourth pregnancies had died of erythroblastosis. Furthermore, in view of the significant rise in antibody titer, the expected infant would undoubtedly be Rh positive and stillborn if the pregnancy were allowed to go to term.

Procedure. A male infant weighing 5 lbs., 6 oz. was delivered by cesarean section six weeks before term. At birth the cord was seen to be bile-stained and the infant was pale and had a weak cry. Blood was taken

* That this was not an artefact was proved by demonstrating that it was possible to distinguish Rh-positive and Rh-negative bloods by the acacia conglutination method, using the infant's serum, diluted 1 to 8 with saline solution, as the testing serum.
† Subsequent experience has shown that it is not uncommon for jaundice to increase for a day or two after the exchange transfusion before subsiding. This may be due to liver damage sustained before the institution of treatment.
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for subsequent examination, but the exchange transfusion was carried out without delay. A total of 420 cc. of blood was withdrawn and 500 cc. injected. The baby withstood the procedure well. Subsequent tests showed that at birth, the hemoglobin concentration was 11.7 grams per 100 cc., the red blood cell count 252 million per cu. mm. with 18 nucleated red blood cells per 100 white cells on the smear. The total white blood count was 23,200 per cu. mm. The icterus index at birth was 70 units. As expected, the baby was Rh positive, the complete classification being OMNRh1rh.

Results. Following the transfusion the hemoglobin concentration was 19.8 grams per cent, and differential agglutination showed that an exchange of about 90 per cent had been accomplished. The icterus deepened on the second day of life although the baby seemed to be clinically well. There was no hepatomegaly or splenomegaly. On the third day of life the baby became intensely jaundiced. The icterus index had risen to 110 units, and the infant became lethargic and refused its feedings. In the latter part of the day, brawny edema of both lower extremities became evident. The hemoglobin concentration had now fallen to 14.7 grams per cent. The subsequent course was downhill. The temperature fell to subnormal levels, the baby refused feedings and became dehydrated. Despite intravenous fluids he failed to improve. On the fifth day of life the temperature rose to 103.5 F. and death ensued.

Autopsy report. Kernicterus; hepatosplenomegaly; necrosis of Hassel's corpuscles; hemorrhage into lungs; large areas of necrosis in the liver; islands of hematopoiesis in the liver, spleen and adrenals.

As is usual in many cases of erythroblastosis, the condition of this infant appeared to be excellent at the time of birth and immediately thereafter. We expected, therefore, that if the progress of the disease could be arrested by exchange transfusion this infant would survive. The death of this baby led us, in subsequent cases, to remove half of the plasma from donor's blood and replace it with saline, thus reducing the conglutinin content of the infused material and favoring hemolysis instead of clumping. The promise of this procedure was not fulfilled and it has therefore been abandoned. We have now further changed our procedure by using 1,000 cc. of blood instead of 500 cc. in the more severe cases, and our limited experience up to the present time indicates that many more of these severe cases can be saved with this modification, which ensures an exchange of 98 per cent of the infant's blood instead of only 87 per cent, thus obviating any possibility of further clumping or hemolysis. Even this modification is not universally successful as will be seen from the case presented below.

Case 12b.—This infant was the sibling of case 10a. The mother became pregnant again about six months after delivering the baby just described and her blood was carefully followed with repeated antibody titrations prior to delivery. The results of these tests are shown in table 12.

Prognosis. In view of the rising titer of antibodies and the history of the loss of three previous infants from erythroblastosis, the prognosis for the expected child appeared to be hopeless if the pregnancy were permitted to go to term; in fact, the fetus was expected to die in utero before the end of the eighth month. The only chance for survival was to deliver the baby while it was still alive and perform a massive exchange transfusion immediately after birth. Even at this time the manifestations were apt to be severe, so that the prognosis was grave.

Procedure. Cesarean section was performed six weeks before term. On exposing the uterus a small herniation the size of a walnut was found in the anterior uterine wall. This was covered only with peritoneum and was filled with blood.† On palpation, the hernia ruptured and bled profusely and the

* Actually, the cells failed to clump in anti-RhO serum, due to coating of the red cells by blocking antibodies.
† In view of this defect in the uterine wall, the patient might have died of a ruptured uterus had she been permitted to go into labor. The development of the defect with the resulting detachment of the underlying placenta may account for the rise in the maternal antibody titer, as such a defect would permit fetal blood to enter the maternal circulation and stimulate the production of additional antibodies.
operation was completed rapidly by extending the incision through the herniation. The infant, on delivery, weighed 5 pounds and 1 ounce and exhibited extreme pallor. Respirations were shallow and infrequent and a moderately large amount of blood and mucus had to be aspirated from the pharynx and trachea. Before the cesarean operation, two donors belonging to group O, type Rh had been bled of 500 cc. each, and this blood was ready for immediate transfusion. Within a few minutes the baby was given 100 cc. of blood and showed marked improvement in its general condition. It did, however, become cyanotic when oxygen was withheld. Exchange transfusion was then completed with the administration of a total of 1,000 cc. of blood and the removal of 950 cc. Throughout the procedure the baby required frequent aspiration and continuous oxygen inhalation. Fifteen cc. of 10 per cent calcium gluconate were given in divided doses of 5 cc. each during the procedure, which took a total of two hours. On being returned to her incubator the infant appeared to be quite well.

Results. During the next twenty-four hours the baby was fairly active. She had one period of apnea which responded to artificial respiration and she also exhibited a few tremors which responded to the intravenous administration of calcium gluconate. On the morning following the procedure, when the baby was about 24 hours old, she suddenly expired.

Laboratory studies done on the cord blood obtained at birth showed: hemoglobin concentration, 5.8 grams per cent; red blood cells, 1.5 million per cu. mm.; white blood cells 4,800 per cu. mm.; polys, 33%; myelocytes, 2; lymphocytes, 61; monocytes 3; eosinophiles, 1. There were 45 nucleated red blood cells per 100 white blood cells on the smear. The icterus index was 52 units. The albumin-plasma conglutination test for coating of the infant’s cells was positive. The baby’s group was OMrh,rh.

After the transfusion the hemoglobin concentration of the infant’s blood was 13.2 grams per 100 cc. and there were 114 nucleated red blood cells per 100 white blood cells.

At autopsy the liver was found to be greatly enlarged with large areas of necrosis, so that there is little doubt that this infant died as the result of damage caused by the maternal antibodies while the fetus was still in utero. It may still be possible, we feel, to save some severely affected infants with less involvement of the liver but who would otherwise die, if the hemoglobin concentration is maintained at normal levels by allowing a larger margin of infused blood over that removed. In this case, a margin of only 50 cc. was allowed and the hemoglobin concentration was only 13.2 grams per cent following the transfusion. We have subsequently found that when a 100 cc. margin instead of 50 cc. is allowed in an exchange transfusion of 1,000 cc. one is more likely to attain a normal hemoglobin concentration of the newborn, namely, about 16 grams. When the patient is extremely anemic as this infant was, a margin as great as 150 cc. is desirable in order to correct the reduction of blood volume usually present in such cases.18
ERYTHROBLASTOSIS AND EXCHANGE TRANSFUSION

Case I. This infant was born in a city 250 miles away and was not under our complete management at any time. The only data available to us antenatally was that the mother was Rh negative and we were told that her serum contained Rh agglutinins in a titer of 64 units shortly before birth. The baby became extremely jaundiced by the fourth day of life; at this time it was lethargic and cyanotic, and had to be placed in an oxygen tent. Exchange transfusion was then performed by us at the request of the attending physician, as a measure of last resort. The infant seemed to be improved immediately following the procedure, but died about five hours following its completion.

Case II. The mother of this patient was first seen by us two years after her fourth pregnancy. Her obstetrical history at that time was as follows. Her first pregnancy terminated with the birth of a male infant who was cyanotic, required resuscitation and lived for only two days. Her second pregnancy yielded a normal male infant who is alive and well. Following this she gave birth to a full term male infant who developed jaundice and lived for only twenty-five hours. Her fourth pregnancy yielded a stillbirth two weeks before term.

Findings. Grouping and Rh-Hr tests done on the father, mother and living child gave the results shown in table 13.

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group and</th>
<th>M-N type</th>
<th>Rh-Hr type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>O</td>
<td>M</td>
<td>Rh_Rh2</td>
</tr>
<tr>
<td>Mother</td>
<td>A, M</td>
<td>M</td>
<td>rh</td>
</tr>
<tr>
<td>Son</td>
<td>A1</td>
<td>M</td>
<td>Rh1</td>
</tr>
</tbody>
</table>

Test for Rh antibodies on the mother's serum gave the following results: Agglutination test—negative; Blocking test—positive, 2 units; Plasma conglutination test—positive, 30 units. These results confirmed the diagnosis of erythroblastosis as the cause of the death of the third infant, and as the cause of the stillbirth which occurred in the fourth pregnancy. In view of the presence of a high titer of univalent antibodies, and the fact that the husband belonged to type Rh,Rh2, every child of this couple would almost surely be Rh positive and stillborn, so the parents were advised against further pregnancies.

The mother was seen again in the sixth week of her fifth pregnancy and from that point on repeated titrations were done until delivery. The results of these studies are shown in table 14. At the time that the last antibody test was done, examination by the attending obstetrician revealed that hydramnios had developed.

Prognosis. In view of the high titer of univalent antibodies and the development of hydramnios indicating fetal pathology, there was little hope of saving this baby unless delivery was carried out immediately and exchange transfusion performed. Intrauterine death seemed to be imminent if the pregnancy were to be allowed to continue for even a few more days.

Procedure. Delivery by cesarean section was carried out at thirty-six weeks. The infant was pale and
icteric at birth and weighed 5 pounds, 8 ounces. Blood was taken for tests to be carried out subsequently and immediate exchange transfusion was performed, using fresh citrated blood from an A, Rh donor. One half of the plasma was removed from the donor's blood and replaced by an equal volume of normal saline. Over a period of 90 minutes, 440 cc. of blood were injected and 380 cc. removed. The baby withstood the procedure well but was having respiratory difficulty when it was sent to the nursery.

**Results.** The hemoglobin concentration was 9.0 grams per cent at birth with a red blood cell count of 2.2 million per cu. mm. The infant belonged to group O, type M, type Rh1rh. The conglutination test for coating of the infant's erythrocytes were positive, and free univalent antibodies could also be detected in the baby's serum.

Following the transfusion the hemoglobin concentration of the blood was 9.4 grams with a red blood cell count of 3.9 million per cu. mm. There were 164 nucleated red blood cells per 100 white blood cells on the smear. For two days the jaundice deepened gradually and the baby became lethargic and began to take its feedings poorly. On the third day of life the hemoglobin concentration had risen to 10.6 grams per cent, with a red blood cell count of 4.7 million, and there was still 100 nucleated red blood cells per 100 white cells on the smear. The jaundice deepened, the infant began to ooze blood from the mouth, developed respiratory distress and expired.

Through mischance this baby was left with a hemoglobin concentration of only 9.4 grams per cent at the end of the procedure, and this, we believe, contributed to its death. While in other cases following the exchange transfusion the erythroblasts quickly disappeared from the baby's blood stream, in this case they increased in number, possibly due in part to the anemia. A sample of blood obtained post-mortem showed twice as many Rh-positive cells as the immediate post-transfusion sample, while in our successful cases differential agglutination tests show no Rh-positive blood cells on the third day. The increase in the proportion of the Rh-positive cells nullified the procedure, and prevented recovery of the baby.

**Case 13.** The mother of this patient was first seen by us in the twenty-fourth week of her second pregnancy because she had been found to be Rh negative in routine prenatal tests done elsewhere. Her first pregnancy had terminated spontaneously at term four years before with the birth of a male infant who is now well. This child had no anemia or jaundice. There was no history of the mother having had a transfusion or injection of blood or plasma.

**Findings.** Grouping and Rh-Hr tests done on the father, mother, and son gave the results shown in table 15.

**Tests for antibodies were done on the mother's serum at intervals during the remainder of her pregnancy with the results shown in table 16.**

**Prognosis.** These results indicated that the mother had become strongly sensitized to the Rh factor with antibodies predominately of the bivalent type, and that the infant would probably have severe erythroblastosis.

**Procedure.** Plans were made to deliver the baby prematurely and perform an immediate exchange transfusion. However, the mother went into labor spontaneously in the thirty-fifth week of pregnancy and delivered a female infant who weighed 5 pounds, 15 ounces, was pale, but not icteric and could be resuscitated only with great difficulty. Immediate exchange transfusion was carried out with the administration of 560 cc. of blood from a donor who belonged to group O, type rh, and the removal of 460 cc. of blood. The baby withstood the procedure well.

**Results.** Examination of the infant's blood taken immediately after birth showed the hemoglobin concentration had been only 4.3 grams per cent. The albumin-plasma conglutination test for coating of the infant's cells was positive and the serum of the cord blood showed the presence of free Rh antibodies in a titer of 3 units by the albumin-plasma technic. On the day following the transfusion the hemoglobin concentration of the blood was 13.5 grams, the red blood cell count 4.1 million per cu. mm., and the white cell count 10,650. There were 310 nucleated red blood cells on the smear. The infant on that day began to show slight jaundice, there was some edema of the extremities and respirations were grunting and rapid. Fine rales were audible throughout the entire chest, and cyanosis developed when oxygen
therapy was discontinued for feedings. Forty-eight hours after the procedure the picture became alarming. The liver and the spleen were both firm and readily palpable about three centimeters below the costal margins, petechiae were present over the shoulders and extremities, and marked jaundice had developed. The hemoglobin concentration was now 13 grams per cent, and there were 350 nucleated red blood cells per 100 white blood cells on the smear. The infant was given a transfusion of 60 cc. of group O, type rh blood and seemed to show some improvement for several hours. On the third day of life, however, dyspnea became more severe, the jaundice appeared to be deeper and the child refused all of its feedings. Blood taken several hours before death showed a serum bilirubin of 11.2 mg. per cent, and a prothrombin time of over three minutes as compared with the control of twelve seconds.

The findings at autopsy were kernicterus, cholemic nephrosis, and pulmonary congestion, edema and atelectasis, with foci of hematopoiesis in the liver and spleen.

Case 14. This case is reported in detail elsewhere.

Case 15.—This infant was first seen by us a few hours after birth because of severe anemia. Delivery had been spontaneous and at term. Pallor was noted immediately, and the amniotic fluid was seen to be yellow. The infant's hemoglobin at birth was .8 grams per cent with a red blood cell count of 1.1 million. This was the mother's first pregnancy. She had no history of having had any abortions or miscarriages. Ten years before she had had poliomyelitis and was given a blood transfusion at that time.

Findings. Grouping and Rh-Hr tests as subsequently determined on the mother, father and the newborn infant gave results shown in table 17.

Tests done on the mother's serum for the presence of antibodies showed that the blocking test was positive in a titer of 4 units, while the albumin-plasma conglutination technic gave a titer of 40 units. Coombs' antiglobulin test for coating of the baby's erythrocytes was positive, and the infant's plasma contained free univalent antibodies in a titer of 40 units by the albumin-plasma conglutination technic. The icterus index of the baby's serum was 40 units.

Prognosis. Although the above information was not available to us at the time that the baby was first seen, it was clear that the child was severely affected with erythroblastosis, and the prognosis was very poor.

Procedure. Exchange transfusion was performed about five hours after birth. Because of the need for haste, group O, type rh bank blood was used. One-third of the plasma was removed and replaced with an equal quantity of normal saline. The infant received 500 cc. of blood while 450 cc. were removed.

Results. There was an immediate improvement in the baby's condition following transfusion, but on
the following day, the patient again looked pale and was given another 75 cc. of blood from a donor who belonged to group O, type rh. On the third day following the exchange transfusion jaundice developed and deepened rapidly. The hemoglobin concentration had now fallen to 10.1 grams per cent from the level of 12.3 grams that was present immediately following the exchange transfusion, and a second supplementary transfusion of 75 cc. of fresh blood was given. Progress was not satisfactory, however. The icterus deepened, the liver and spleen became enlarged and the baby became lethargic and had intermittent periods of cyanosis. At the end of one week the temperature rose to 103 F. and the anterior fontanelle was found to be bulging. Spinal tap revealed a canary yellow fluid that contained 7 white blood cells and 5 red blood cells per cu. mm. The Pandy reaction was 4 plus and the qualitative sugar reaction on the spinal fluid was 3 plus. The blood culture was positive for staphylococcus aureus. Despite penicillin therapy, a large abscess, which yielded 8 cc. of purulent fluid on incision and drainage, appeared over the upper thoracic vertebrae. Culture of this material was also positive for staphylococcus aureus. The baby developed diarrhea and scattered indurated areas over the body on the twenty-ninth day of life and expired the following day.

Autopsy revealed bacteremia; pyohydrocephalus; abscesses in the thyroid, heart, kidney and the brain; kernicterus; cirrhosis of the liver; sepsis thrombophlebitis of the pulmonary veins; and focal pneumonia.

**Table 17**

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group</th>
<th>M-N type</th>
<th>Rh-Hr type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>A1</td>
<td>MN</td>
<td>Rh,Rh,R'h'</td>
</tr>
<tr>
<td>Mother</td>
<td>A1</td>
<td>N</td>
<td>rh</td>
</tr>
<tr>
<td>Baby</td>
<td>O</td>
<td>MN</td>
<td>Rh,rh</td>
</tr>
</tbody>
</table>

**Cases of Moderate Severity**

CASE 16.—This case has been reported in detail elsewhere.2

CASE 17.—The mother of this patient was first seen by us in the first trimester of her third pregnancy. She had delivered a normal boy seven years previously who is living and well. Her second child, a boy, was born three years ago. He was normal at birth, but on the second day of life was seen to be jaundiced. The hemoglobin concentration of his blood was 7.3 grams per 100 cc. and the red count was 2.3 million per cu. mm. He was found to be Rh positive while the mother was Rh negative. Over a period of twelve days he received three transfusions of 75 cc. each of group A, Rh-negative blood without showing any appreciable rise in hemoglobin concentration or red blood count. On the fifteenth day of life, however, he was given 10 cc. of washed mother's red cells in two portions and his hemoglobin concentration rose to 12 grams per cent. From this point onward his recovery was uneventful. At the time when his jaundice was at its peak the van den Bergh reaction showed a concentration of 46.7 mg. of bilirubin in his blood.

**Findings.** Grouping and Rh-Hr tests done on the family gave the results in table 18.

At the time of the first test for Rh antibodies in the mother's serum, no agglutinins were demonstrable, but univalent antibodies were shown to be present in a titer of 16 units by the plasma conglutination technic. Anti-A and anti-B titrations on the mother's plasma by both the agglutination and conglutination technics were within normal limits. By the middle of the third trimester of pregnancy, however, Rh agglutinins could be demonstrated in a titer of 1:16 units, while the conglutination titer had fallen to 3 units. A slight rise of both anti-A and anti-B titers above the normal was found at this time.

**Prognosis.** Since the anti-Rh titer had fallen it could be confidently predicted that a viable infant would be obtained, even though the infant was almost certain to be Rh positive and therefore erythroblastotic. If the baby belonged to group A, the presence of mild sensitization to the A agglutinogen might further complicate the picture, but probably not to a serious degree.

**Procedure.** The baby was delivered at term and was observed for twelve hours. Studies done during this time showed that the hemoglobin concentration of the blood was 14.5 grams per 100 cc.; the red blood
count was 4.7 million cells per cu. mm. and the white blood count 26,100 per cu. mm. There were 30 nucleated red blood cells per 100 white blood cells and the icterus index of the cord serum was 12 units. The infant proved to belong to group A₂MNRh₁Rh₂. After twelve hours the icterus index had risen to 24 units, and the baby began to show slight clinical jaundice.

Exchange transfusion was carried out using a donor that belonged to group A₁MNrh. To reduce the concentration of the conglutinin in the infusion material, half of the plasma was removed from this blood and replaced with saline. Ten cc. of Witebsky group substances were then added to neutralize the alpha antibodies present in the infant’s body and derived from the mother. The usual procedure was then carried out, 500 cc. of blood being injected and 460 cc. simultaneously removed.

Results. The hemoglobin concentration was 13.5 grams per cent on the day following the transfusion. By the sixth day it fell to 8.8 grams per cent and another transfusion of 70 cc. of blood, this time from an A₂rh donor was given. The hemoglobin rose to 11.7 grams per cent but over the next five days fell again to 8.7 grams. Following a final transfusion of 60 cc. of A₁Rh blood the hemoglobin concentration became stabilized and the baby was discharged from the hospital. The van den Bergh reaction, which was indirect, showed a concentration of 5.7 mg. of bilirubin per 100 cc. at 3 days of age, and fell steadily to normal during the hospital stay of three weeks. At the age of 2 months, the hemoglobin concentration was 10.7 grams per cent and the baby was well. Some splenic enlargement was noted at that time, but was no longer demonstrable 6 months later. At the age of one year the child was perfectly normal in every respect. He stood and was beginning to take a few steps. Language development was normal for that age.

This case is unusual in that the patient required two supplementary simple transfusions after the exchange transfusion, while in typical cases the exchange transfusion alone is sufficient to bring about a cure. This may be ascribed to the fact that the mother was sensitized to the agglutinogen A as well as Rh, and especially to the use of blood of subgroup A₁ for the exchange transfusion instead of blood of subgroup A₂ or group O. The titer of alpha antibodies in the maternal serum was only slightly elevated, so that ordinarily one would expect the alpha antibodies passing into the fetal circulation to be completely neutralized by the A substance in its blood and tissues, leaving no free alpha antibody to affect the transfused group A blood cells. In this case, however, the baby belonged to subgroup A₂, so its tissues and blood were capable of neutralizing only the common alpha antibody, leaving alpha₁ antibody free to lyse the transfused A₁ cells. While this prolonged the baby’s illness, recovery readily resulted after two simple, supplementary transfusions of blood of subgroup A₂.

**Table 18**

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group and subgroup</th>
<th>M-N type</th>
<th>Rh-Il type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>A₂</td>
<td>MN</td>
<td>Rh₁Rh₂</td>
</tr>
<tr>
<td>Mother</td>
<td>O</td>
<td>N</td>
<td>rh</td>
</tr>
<tr>
<td>1st son</td>
<td>O</td>
<td>MN</td>
<td>Rh₁</td>
</tr>
<tr>
<td>2nd son</td>
<td>A₂</td>
<td>N</td>
<td>Rh₁</td>
</tr>
</tbody>
</table>

was no longer demonstrable 6 months later. At the age of one year the child was perfectly normal in every respect. He stood and was beginning to take a few steps. Language development was normal for that age.

This case is unusual in that the patient required two supplementary simple transfusions after the exchange transfusion, while in typical cases the exchange transfusion alone is sufficient to bring about a cure. This may be ascribed to the fact that the mother was sensitized to the agglutinogen A as well as Rh, and especially to the use of blood of subgroup A₁ for the exchange transfusion instead of blood of subgroup A₂ or group O. The titer of alpha antibodies in the maternal serum was only slightly elevated, so that ordinarily one would expect the alpha antibodies passing into the fetal circulation to be completely neutralized by the A substance in its blood and tissues, leaving no free alpha antibody to affect the transfused group A blood cells. In this case, however, the baby belonged to subgroup A₂, so its tissues and blood were capable of neutralizing only the common alpha antibody, leaving alpha₁ antibody free to lyse the transfused A₁ cells. While this prolonged the baby’s illness, recovery readily resulted after two simple, supplementary transfusions of blood of subgroup A₂.

**Case 18.**—No antenatal tests had been done in this case. The infant was referred to us when she was 9 hours old because of jaundice and anemia. She was the product of the second pregnancy. The first pregnancy was uncomplicated and resulted in the birth of a normal child who is living and well today. The
ALEXANDER S. WIENER AND IRVING B. WEXLER 2

patient was born at term and was definitely icteric at birth. At the age of 5 hours the hemoglobin concentration was only 8.1 grams per cent and there were 15 normoblasts per high power field on the blood smear. The baby was given 80 cc. of group O, type rh blood before she was referred to us.

Findings. Grouping and Rh-Hr tests on the family gave the results shown in table 19.

Antibody tests done on the mother's serum showed that a mixture of both bivalent and univalent antibodies were present. The agglutination test showed a titer of Rh antibodies of 12 units, while the titer by the albumin-plasma conglutination technic was 18 units. The serum of the infant was shown to contain free univalent Rh antibodies by the albumin-plasma conglutination test, which was positive to a dilution of 1:2.

Prognosis. In view of the significant antibody titer and deepening jaundice (icterus index 2.2.0 units), this was a severely affected infant who required immediate and vigorous treatment.

Procedure. Exchange transfusion was carried out twenty-four hours after birth using bank blood from an O, rh donor from which half of the plasma had been removed and replaced by saline. The baby was given 50 cc. of this blood while 50 cc. were removed.

Results. On the day following the transfusion the baby seemed very much improved although the hemoglobin concentration of the blood was only 11.1 grams per cent. At eighteen hours after the procedure the baby again became deeply jaundiced, and edema of the extremities, particularly the legs developed. The spleen and liver were now enlarged and examination of the blood smear revealed that there were 270 nucleated blood cells per 100 white blood cells. At the same time the hemoglobin concentration had fallen to 9.0 grams per cent. This evidence of continued blood destruction was interpreted as being due to the fact that bank blood had been used for the exchange and a further small transfusion of 40 cc. of fresh blood from an O, rh donor was given. The jaundice began to fade on the following day and by the next week had faded completely. The hemoglobin concentration which had risen to 12.7 grams per 100 cc. following the supplementary transfusion was maintained and the baby was discharged from the hospital at the age of two weeks. No further transfusions were necessary. When the baby was last seen at the age of 8 months she was sitting alone and appeared to be normal in every respect.

This is one of the few cases in which a supplementary simple transfusion was necessary after the exchange transfusions were done. This we ascribe to the use of bank blood of uncertain state of preservation. We were compelled to use bank blood in this case because no compatible donor was available, and the baby's critical condition made it imperative to avoid any delay in starting the exchange transfusion. The case demonstrates that for exchange transfusion fresh citrated blood, if available, should be used instead of bank blood because the more satisfactory results with fresh blood more than compensate for its greater cost and inconvenience.

Case 19.—The mother of this infant was first seen by us in the thirty-first week of her fifth pregnancy. Her first pregnancy, four years previously, resulted in the birth of a son who is living and well. Her second pregnancy terminated with the birth of a girl who is also normal. Her third baby, a girl, was well until
2.2. ERYTHROBLASTOSIS AND EXCHANGE TRANSFUSION

the fourth day of life when she became jaundiced and anemic. She received four transfusions of Rh-negative blood over a period of two weeks and made a complete recovery. The birth of this baby was followed by a miscarriage at two months. There was no history of the mother ever having received a blood or plasma transfusion or blood injection.

Findings. Grouping and Rh-Hr tests done on the father, mother, and all the living children gave the results shown in table 20.

Tests for Rh antibodies on the mother's serum showed that while the agglutination test was negative, the titer of univalent antibodies was 4 units as determined by the albumin-plasma conglutination test.

Prognosis. Since the father was almost surely homozygous for the Rh0 factor, the new baby would be expected to be Rh positive and therefore erythroblastotic, though not severely affected in view of the rather low Rh antibody titer of the maternal serum.

Procedure. It was planned to deliver the infant at term and do an exchange transfusion immediately after birth. However, the mother went into labor spontaneously six weeks before term and delivered a 5 pound premature infant that seemed to be normal. Exchange transfusion was performed using 380 cc. of group O, type rh bank blood for the infusion and removing cc cc. of blood from the baby. In this particular case the blood vessels were found to be uncommonly small and difficulty was encountered with the bleeding, so that we actually were obliged to fall short of the 500 cc. mark that we had established for ourselves as the minimal goal in doing an exchange transfusion.

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group</th>
<th>M-N type</th>
<th>Rh-Hr type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>O</td>
<td>MN</td>
<td>Rh1Rh2 or Rh0</td>
</tr>
<tr>
<td>Mother</td>
<td>O</td>
<td>N</td>
<td>rh</td>
</tr>
<tr>
<td>Son</td>
<td>O</td>
<td>N</td>
<td>Rh1, Rh0</td>
</tr>
<tr>
<td>1st daughter</td>
<td>O</td>
<td>MN</td>
<td>Rh1, Rh0</td>
</tr>
<tr>
<td>2nd daughter (erythroblastotic)</td>
<td>O</td>
<td>MN</td>
<td>Rh1, Rh0</td>
</tr>
</tbody>
</table>

Results. The baby did well from the clinical point of view, that is, feedings were taken normally and the weight gain was satisfactory. The baby did not develop any jaundice. However, the hemoglobin concentration, which was 16 grams per cent at birth, was only 13.4 grams per cent on the day following the transfusion. Over the next eleven days the hemoglobin concentration fell to 10.5 grams per cent and the infant was discharged. Four days later the hemoglobin concentration of the blood had fallen to 8.0 grams and the patient was transfused with 55 cc. of group O, type rh bank blood. Two days later the transfusion was repeated and the hemoglobin concentration from that point onward was maintained at over 11 grams per cent. The child's subsequent course has been uneventful, though there is some slight doubt in the mind of the mother that he is as bright as his siblings.

Case 20.—This one day old female infant was referred to us because of jaundice and anemia of six hours' duration. She was the second child. The first, a girl, was 3½ years of age and was well. The mother had never been transfused and had never had any stillbirths or miscarriages.

Findings. When first seen the infant was deeply jaundiced and had numerous petechiae on the forehead. The liver and spleen were not enlarged. The hemoglobin concentration of the blood was 11.3 grams per cent and red blood count was 3.4 million per cu. mm. The icterus index was 111 units.

Grouping and Rh-Hr tests done on the mother, father, and the patient gave the results shown in table 21.

Antibody tests done on the mother's serum were positive to 1½ units by the agglutination technic, and also by the plasma conglutination and albumin-plasma technics. Conglutination tests for coating of the baby's erythrocytes were negative, and no free Rh antibody was demonstrable in the infant's serum.
Prognosis. If one could depend entirely upon the maternal antibody titer as a criterion, this could be regarded as a case with only mild sensitization and therefore with a good prognosis. However, the severe clinical condition of the infant, with deep jaundice and hemorrhagic phenomena called for more vigorous treatment than simple transfusion. We felt that with exchange transfusion the prognosis would be good and also that the need for repeated transfusions would be obviated.

Procedure. Group O, type rh bank blood was used. One half of the plasma was removed and replaced with normal saline. The baby received 490 cc. while 450 cc. was removed over a period of about ninety minutes. The baby withstood the procedure well.

Results. On the following day the hemoglobin concentration of the blood was 13 grams per cent and the red blood cell count was 4.15 million per cu. mm. There were 3 normoblasts per 100 white blood cells on the smear. The jaundice faded in three days and the child was discharged as well.

CASE 1. The mother of this patient was first seen in the thirty-sixth week of her third pregnancy. She had had a spontaneous miscarriage at 4½ months two years previously, and a spontaneous abortion at 23 months about one year later. Three years ago she was operated upon for volvulus of the small bowel, and had had 8 feet of ileum removed. She was given a blood transfusion postoperatively.

Findings. Grouping and Rh-Hr tests done on the prospective parents gave the results shown in table 2.1. Test for Rh antibodies done on the mother's serum gave the results shown in table 2.2. In view of the difference in the blood groups, titrations were also carried out for alpha and beta antibodies in the mother's serum. The results of these tests are shown in table 2.3.

Prognosis. From the results of the Rh antibody tests, it was evident that the mother was definitely, though weakly, sensitized to the Rh factor, and that it was likely that the expected infant would have mild erythroblastosis.

Procedure. In order to spare the infant prolonged contact with the antibodies it was planned to induce labor about two weeks before term, and treat the infant with exchange transfusion but only if signs of erythroblastosis developed. The obstetrician elected to deliver the patient by cesarean section, and this was carried out at the end of the thirty-eighth week of pregnancy.

The infant, a male, weighed 6 pounds and 1 ounce and appeared to be normal. There was no pallor, jaundice or hepatosplenomegaly. The hemoglobin concentration of the blood was 16.9 grams per cent and the red blood cell count was 4.14 million per cu. mm. There was 8 normoblasts per white blood cells on the smear. The icterus index was 14 units and the baby’s blood typed as AMNRh₁Rh₂.

Twenty-four hours after birth, slight jaundice was noted and blood studies showed that the hemoglobin concentration had now fallen to 13.5 grams per cent with a red blood cell count of 3.4 million per
ERYTHROBLASTOSIS AND EXCHANGE TRANSFUSION

cum. mm. Five normoblasts per 100 white blood cells were seen on the smear. No hepatic or splenic enlargement had developed. The serum bilirubin concentration was 9.5 mg./100 cc.

Exchange transfusion was performed with the administration of 520 cc. blood from an A2Nrh donor, and the removal of 470 cc. The baby tolerated the procedure well.

Results.—On the day following the procedure the hemoglobin concentration of the blood was 13 grams per cent and the red blood cell count 4.18 million per cu. mm. The jaundice was unchanged and the infant appeared well.

At this time there was an outbreak of diarrhea on the ward, and despite all precautions the patient developed loose watery stools and rapidly become dehydrated and acidotic. The CO₂ content of the blood fell to 22 volumes per cent and the patient was treated with starvation and parenteral fluids. Blood culture was negative, and the stool culture was negative for pathogens. Feedings were resumed after twenty-four hours when the character of the stools returned to normal. Two days after the onset of diarrhea the hemoglobin concentration of the blood had fallen to 11 grams per cent and the red blood cell count to 3.9 million per cu. mm. The patient was transfused twice with 60 cc. blood from group O, type rh donors, and after the diarrhea was completely controlled was discharged 17 days after admission.

When seen at the age of 2 months he was well; he weighed 10 pounds and was not jaundiced.

Table 23

<table>
<thead>
<tr>
<th>Time of test</th>
<th>Titer by agglutination technic</th>
<th>Titer by albumin-plasma technic</th>
</tr>
</thead>
<tbody>
<tr>
<td>36th week</td>
<td>0</td>
<td>doubtful</td>
</tr>
<tr>
<td>37th week</td>
<td>0</td>
<td>1/2</td>
</tr>
</tbody>
</table>

Table 24

<table>
<thead>
<tr>
<th>Time of test</th>
<th>Agglutination technic</th>
<th>Plasma-conglutination technic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-A</td>
<td>Anti-B</td>
</tr>
<tr>
<td>36th week</td>
<td>96</td>
<td>60</td>
</tr>
<tr>
<td>37th week</td>
<td>40</td>
<td>48</td>
</tr>
</tbody>
</table>

Mild Cases

CASE 22.—The mother of this infant was first seen in the thirty-fifth week of her third pregnancy. Her first pregnancy had terminated prematurely with the birth of a normal female child. Her second infant, a female, was carried to term and was delivered normally. Both of these children are living and well. There was no history of the mother ever having received a transfusion or blood injection.

Findings. Grouping and Rh-Hr tests done on the father, mother, and both children gave the results shown in table 25.

The results of the antibody titrations done on the mother's serum are given in table 26.

Prognosis. These findings indicated that the expected infant would almost surely be Rh positive, and therefore erythroblastotic, since the mother was sensitized to the Rh factor. However, since the Rh agglutinins in the maternal serum interfered with the determination of the titer of univalent antibodies, if any, the severity of the manifestations in the baby were not predictable.

Procedure. Labor was induced in the thirty-ninth week of pregnancy and the infant, a female, was immediately treated by exchange transfusion. Over a period of one hour 100 cc. of blood from an OMrh donor were injected and 480 cc. removed. The baby stood the procedure well.

Results. No clinical symptoms of erythroblastosis ever developed. The baby's hemoglobin concentration at birth was 17.4 grams per cent and the red blood cell count 4.3 million. There were no erythroblasts on the smear. Coating test on the baby's red blood cells (OMNRh2) was negative. On the day following
the transfusion the hemoglobin concentration was 15.5 grams. Mild icterus made its appearance on the second day of life, but faded rapidly thereafter. The baby was discharged on the fourth day.

Case 2.—This was the mother’s second pregnancy. Her first pregnancy was normal and went to term, but labor was prolonged and the infant was delivered by high forceps. The child had no jaundice or anemia, but its neonatal period was complicated by convulsions said to be due to cerebral hemorrhage attendant upon the traumatic delivery. Routine Rh tests done in the course of the second pregnancy revealed the mother to be Rh negative and sensitized to the Rh factor.

Findings. Grouping and Rh-Hr tests were done on the family, and the results are shown in table 2.7.

Antibody tests on the mother’s serum, done at thirty-six weeks, were positive to a titer of 1 unit by the agglutination technic and to a titer of 14 units by the albumin-plasma conglutination technic.

**Table 2.5**

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group and subgroup</th>
<th>M-N type</th>
<th>Rh-Hr type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>O</td>
<td>N</td>
<td>Rh<em>Rh</em></td>
</tr>
<tr>
<td>Mother</td>
<td>O</td>
<td>M</td>
<td>rh</td>
</tr>
<tr>
<td>1st daughter</td>
<td>O</td>
<td>MN</td>
<td>Rh<em>Rh</em></td>
</tr>
<tr>
<td>2nd daughter</td>
<td>O</td>
<td>MN</td>
<td>Rh<em>Rh</em></td>
</tr>
</tbody>
</table>

**Table 2.6**

<table>
<thead>
<tr>
<th>Week of pregnancy</th>
<th>Titer by agglutination technic</th>
<th>Titer by albumin-plasma technic</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 weeks</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>39 weeks</td>
<td>36</td>
<td>20</td>
</tr>
</tbody>
</table>

**Table 2.7**

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group and subgroup</th>
<th>M-N type</th>
<th>Rh-Hr type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>A</td>
<td>MN</td>
<td>Rh<em>Rh</em></td>
</tr>
<tr>
<td>Mother</td>
<td>B</td>
<td>M</td>
<td>rh</td>
</tr>
<tr>
<td>First child</td>
<td>O</td>
<td>M</td>
<td>Rh<em>Rh</em></td>
</tr>
</tbody>
</table>

Prognosis. Since the husband was almost surely homozygous for the Rh0 factor every child of this couple was bound to be Rh positive. In view of the moderately high titer of univalent antibodies in the mother’s circulation an erythroblastotic infant with manifestations of only moderate severity was to be expected.

Procedure. In order that the infant be spared unnecessarily prolonged exposure to the Rh antibodies, delivery was carried out about 10 days before term. This was done by cesarean section because of the mother’s contracted pelvis. Sterilization by ligation of the fallopian tubes was also done at this time. At birth the infant appeared to be perfectly normal clinically. The baby was grouped and was found to belong to group AB, type Rh*Rh*, and so was Rh positive as expected. Exchange transfusion was performed using blood from a group AB, type rh donor. Over a period of forty minutes 560 cc. of blood were injected while 550 cc. were removed. The baby withstood the procedure very well. Studies done on the cord blood showed a hemoglobin concentration of 18.8 grams per 100 cc. with a red blood count of 5.78 million. No nucleated red cells were seen on the smear. However, the conglutination test for coating of infant’s red cells by antibodies was positive.
ERYTHROBLASTOSIS AND EXCHANGE TRANSFUSION

Results. The baby never developed either jaundice or anemia. It was discharged from the hospital on the 10th day and required no further transfusions. Differential agglutination studies showed that a 90 per cent replacement had been effectuated. At 3 weeks postpartum the titer of anti-Rh agglutinins in the mother's serum had risen to 88 units while the antibody titer was shown to be 175 units by the albumin-plasma conglutination technic.

In most sensitized Rh-negative women, there is a rise in Rh antibody titer following the birth of the baby, probably due to leakage of infant's blood into the maternal circulation during labor. The case just described demonstrates that such a rise also occurs when delivery is accomplished by cesarean section, so that operative delivery does not prevent maternal sensitization. In view of the very high Rh antibody titer of the maternal serum after delivery and the fact that the husband belonged to type Rh, Rh, it seems obvious that every future pregnancy would almost surely result in death of the fetus before it reached the stage of viability.

Case 24.—This infant was referred to us at the age of 2 days because of jaundice which had first been noticed when the baby was 17 hours old. The mother had had two previous pregnancies, and both children were alive and well. The first had been entirely normal during its neonatal period, while the second had developed jaundice on the second day of life and recovered after a brief illness. There was no history of the mother's ever having received any blood transfusions. Antenatal Rh testing had not been done.

The patient appeared to be normal at birth, but jaundice was noted on the morning of the second day of life. The hemoglobin concentration was found to be 10.4 grams per cent and the icterus index 50 units. Findings. Forty-eight hours postpartum, grouping and Rh-Hr tests done on the family gave the results shown in table 28.

Antibody studies done on the mother's plasma showed that while no Rh antibodies could be demonstrated by the saline agglutination technic, weak univalent antibodies were present in a titer of 3 units as demonstrated by the albumin-plasma method. Furthermore, univalent antibodies could be demonstrated in the infant's serum also in a titer of 2 units. Since there was a possibility of double sensitization (to A as well as to Rh) the mother's anti-A and anti-B titers were determined. By the agglutination method anti-A was demonstrable in her serum in a titer of 40 units, and anti-B in a titer of 30 units. By the plasma conglutination technic the titer of anti-A was 60 units and anti-B was 70 units.

Prognosis. This then was a case of double, though mild, sensitization to both the Rh factor and the A agglutinogen. If untreated, the infant was bound to develop a mild but progressive anemia that would require several transfusions, if treated in the usual manner. In view of the low antibody titers, there was practically no danger of intravascular clumping.

Procedure. In order to limit the number of transfusions required, an exchange transfusion was decided upon. Four hundred cc. of blood were withdrawn from the infant and simultaneously replaced by 500 cc. of blood from a group A, type rh donor. Following the transfusion, 10 cc. of Witebsky's A and B group
ALEXANDER S. WIENER AND IRVING B. WEXLER

substance* were administered intravenously in order to counteract the action of any anti-A that might have been passively received by the infant from the mother.

Results. The hemoglobin concentration was 12 grams per 100 cc. at the end of the procedure, and differential agglutination tests showed that 90 per cent of the infant's blood cells had been replaced. The icterus index remained at its pretransfusion level for a few days and then slowly subsided. At 3 weeks there was no visible jaundice and the hemoglobin concentration was 8.8 grams per cent. When seen again at 6 weeks of age, the child was well, was developing normally and gaining weight. No hepatic or splenic enlargement was present. When seen again at the age of one year, the child was developing normally both mentally and physically.

Case 25.—The mother of this patient was referred to us in the twenty-second week of her third pregnancy. Her first pregnancy terminated in the fifth month with the birth of a 14 pound stillborn fetus. Her second pregnancy went to term and resulted in the birth of a normal male child who was jaundiced for a day or two but required no treatment and has been well since. The mother had never received any injections of blood or plasma.

Grouping and Rh-Hr tests done on the father, mother and the living child gave the results shown in table 29.

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group and subgroup</th>
<th>M-N type</th>
<th>Rh-Hr type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>A1</td>
<td>M</td>
<td>Rh1Rh2</td>
</tr>
<tr>
<td>Mother</td>
<td>O</td>
<td>M</td>
<td>rh</td>
</tr>
<tr>
<td>Son</td>
<td>O</td>
<td>M</td>
<td>Rh2</td>
</tr>
</tbody>
</table>

Table 29

<table>
<thead>
<tr>
<th>Week of pregnancy</th>
<th>Titration by agglutination technic</th>
<th>Titration by albumin-plasma technic</th>
</tr>
</thead>
<tbody>
<tr>
<td>21st week</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>31st week</td>
<td>0</td>
<td>doubtful</td>
</tr>
<tr>
<td>37th week</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 30

Antibody titrations done on the mother's plasma at intervals during the remainder of her pregnancy gave the results shown in table 30.

Prognosis. Sensitization in this case was mild. Although it could be predicted that the expected infant would have erythroblastosis, the manifestations would probably not be severe.

Procedure. Labor was induced in the thirty-seventh week of pregnancy to limit the period during which the infant would be exposed to the action of the antibodies, especially in view of the rise in titer, and the infant was observed for manifestations of erythroblastosis. The hemoglobin concentration of the blood was 18 grams per cent and the icterus index was 10 units at birth. There was only 1 normoblast per 100 white blood cells on the smear. The baby was typed as group A, MRhhr. A very slight reaction was obtained in the conglutination test for coating of the infant's cells, and the baby's cord serum showed the presence of free Rh antibodies in a titer of only 2 unit by the albumin-plasma technic.

About twelve hours after delivery the icterus index had risen to 20 units and by 24 hours had risen to 65 units. There was no change in the hematologic findings. Exchange transfusion was decided upon in view of the rapidly advancing jaundice. Blood was drawn from an A2Mrh donor into citrate solution.

* This solution was provided through the courtesy of Sharpe and Dohme, Inc.
Half of the plasma was removed and replaced with saline. Five hundred and forty cc. were injected and 480 cc. withdrawn. The baby withstood the procedure well.

Results. At the end of the transfusion the icterus index was 45 units and on the day following had fallen to 30 units. The jaundice subsided rapidly and the baby was discharged from the hospital at the end of one week. At the age of 3 weeks the hemoglobin concentration of the baby’s blood was 14.4 grams per cent. At the age of 3 months the child was doing well, and seemed to be developing normally.

Case 26.—The mother of this infant was first seen by us in the thirty-seventh week of her second pregnancy. Her first pregnancy had terminated with the birth of a male infant who is well. Following the delivery the mother had a pulmonary embolus from which she did not recover for several months. She never had a blood or plasma transfusion. She had been found to be Rh negative by routine antenatal Rh testing, but no antibodies had been found until a few days before she was referred to us.

Findings. Grouping and Rh-Hr tests done on the father, mother, and son gave the results shown in Table 31.

No agglutinins could be detected in the mother’s serum and univalent antibodies of only one unit titer were found to be present by the albumin-plasma technic.

Prognosis. Since the father was almost surely homozygous for the Rh0 factor, the expected infant would be Rh positive. However, the low titer of antibodies in the mother’s serum made it questionable that the infant would be affected by the disease. In fact, if erythroblastosis did develop at all the manifestations would be expected to be very mild.

Procedure. Labor was induced at the end of the thirty-eighth week of pregnancy and a normal appearing baby girl weighing 6 pounds was delivered. The icterus index of the cord blood was 14 units and the hemoglobin concentration of the blood was 12.9 grams per cent with a red blood cell count of 4.33 million per cu. mm. There was one normoblast per 100 white blood cells on the smear. No jaundice or hepatosplenomegaly was noted. The albumin-plasma conglutination test for coating of the infant’s cells was negative, though as predicted the baby was Rh positive (OMNRh,rh).

Twelve hours later the icterus index had risen to 18 units and it was decided that an exchange transfusion be performed. Blood was drawn from a donor who belonged to group O, type rh and one-half of the plasma removed and replaced with normal saline to reduce the conglutinin content. Over a period of one and one-half hours 500 cc. of blood were injected and 450 cc. removed.

Results. Twenty-four hours after the transfusion the hemoglobin concentration of the blood was 16.1 grams per cent and the red blood cell count 5.4 million per cu. mm. The baby did not develop jaundice or anemia while in the hospital and was discharged with the mother on the fourth day. At the age of one week the hemoglobin concentration was 13.8 grams per cent and the red blood cell count 4.66 million. There was no jaundice present clinically, and by differential agglutination the baby’s blood typed as Rh positive (OMNRh,rh). One week after delivery the titer of univalent antibodies in the mother’s serum had risen to 10 units by the albumin-plasma technic. No agglutinins were demonstrated. At the age of one month, the hemoglobin concentration of the infant’s blood had fallen to 8.4 grams, and then rose spontaneously to 9.6 grams at the age of 2 months, and to 12.9 grams per cent by the age of 3 months. Blood typing at this time showed that all the erythrocytes typed as OMNRh,rh, the baby’s original type. The infant’s subsequent course has been uneventful.

In retrospect, we consider this as a case that would have done well with the usual transfusion therapy or might even have recovered without any therapy at all. This case occurred early in our series and we were unduly impressed with the slight anemia and the rise in icterus index that occurred after delivery. Subsequently, we have seen 4 cases which had similar minimal titers of antibodies in the maternal serum. Of these, 2 developed mild clinical signs of erythroblastosis and recovered without therapy. The other 2 had no clinical signs of the disease at all.

Case 27.—The mother of this patient was first seen by us six months after her first pregnancy. This had terminated one month prematurely with a stillborn anencephalic male, and was complicated by placenta previa. Following the delivery she received four transfusions of blood. She had chills and high fever.
following the first two of these, but no reactions to the third or fourth. It is not known whether the blood
she received was selected on the basis of Rh testing.

Findings. Grouping and Rh-Hr tests done on the woman and her husband gave the results shown in
Table 32.

Tests for antibodies done on the wife’s serum showed that while no antibodies could be demonstrated
by the saline agglutination technic, univalent antibodies of 4 units titer were shown to be present by the
plasma conglutination method.

Six months later the antibody studies were repeated, and this time no antibodies could be demonstrated
by either the agglutination or the plasma conglutination technics.

About six months after these tests were done she became pregnant again and the results of antibody
tests done on her serum throughout her pregnancy are shown in Table 33.

**Table 31**

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group and subgroup</th>
<th>Rh-Hr type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>O</td>
<td>Rh(_1)Rh(_1), R'R' or R'r'</td>
</tr>
<tr>
<td>Mother</td>
<td>A(_1)</td>
<td>Rh(_1)Rh(_1), rh, rr, R'r'</td>
</tr>
<tr>
<td>Son</td>
<td>O</td>
<td>Rh(_1)Rh(_1), Rh(_1)Rh, R'r'</td>
</tr>
</tbody>
</table>

**Table 32**

<table>
<thead>
<tr>
<th>Blood of</th>
<th>Group and subgroup</th>
<th>Rh-Hr type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Husband</td>
<td>A(_1)</td>
<td>Rh(_1)Rh(_1), rh, rr, R'r'</td>
</tr>
<tr>
<td>Wife</td>
<td>A(_1)</td>
<td>Rh(_1)Rh(_1), rh, rr, R'r'</td>
</tr>
</tbody>
</table>

**Table 33**

<table>
<thead>
<tr>
<th>Week of test</th>
<th>Titer by agglutination technic</th>
<th>Titer by albumin-plasma technic</th>
</tr>
</thead>
<tbody>
<tr>
<td>9th week</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>22nd week</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>28th week</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35th week</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Prognosis. Delivery was accomplished by cesarean section at the end of the thirty-seventh week of
pregnancy. A blood count was done immediately after birth and showed that the hemoglobin concentra-
tion of the blood was 12.7 grams per cent and the red blood cell count was 3.8 million per cu. mm. There
were 10 nucleated red blood cells per 100 white blood cells on the smear. In view of these findings an
exchange transfusion was carried out with the administration of 500 cc. of group A, type rh blood and
the removal of 455 cc. of infant’s blood.

Results. The infant withstood the procedure well, and on the following day the hemoglobin concentra-
tion was 17.1 grams per cent with a red blood cell count of 5.65 million. The baby never became jaundiced
and was discharged on the eighth day. When seen at the age of 3 months the baby was well, had gained
weight normally and appeared to be alert and active.

Comment

The case histories have been presented in considerable detail because it is only in
relation to the severity of the individual case that the efficacy of the exchange
**ERYTHROBLASTOSIS AND EXCHANGE TRANSFUSION**

<table>
<thead>
<tr>
<th>Case number</th>
<th>Father's Group and Rh-Hr type</th>
<th>Mother's group and Rh-Hr type</th>
<th>Maternal Rh antibody titer (units)</th>
<th>Infant's group and Rh-Hr type</th>
<th>Clinical Summary, see bottom of table</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Agglutination Method</td>
<td>Conglutination Method</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>O Rh, Rh</td>
<td>A1 rh</td>
<td>0</td>
<td>1400 (Bl. 32)</td>
<td>O Rh, rh Died on 2nd day</td>
</tr>
<tr>
<td>2.</td>
<td>O Rh, Rh</td>
<td>A1 rh</td>
<td>0</td>
<td>112 (Bl. 2)</td>
<td>O Rh, rh Died on 3rd day</td>
</tr>
<tr>
<td>3.</td>
<td>A1 Rhi Rh</td>
<td>O rh</td>
<td>0</td>
<td>44 (Bl. 5)</td>
<td>A1 Rhi rh Recovered</td>
</tr>
<tr>
<td>4.</td>
<td>O Rh, Rh</td>
<td>A1 rh</td>
<td>0</td>
<td>30</td>
<td>A1 Rhi rh Recovered</td>
</tr>
<tr>
<td>5.</td>
<td>O Rh, Rh</td>
<td>A1 rh</td>
<td>0</td>
<td>12*,</td>
<td>A1 Rhi rh Recovered</td>
</tr>
<tr>
<td>6.</td>
<td>O Rh, Rh</td>
<td>A1 rh</td>
<td>0</td>
<td>4</td>
<td>O Rh, rh Recovered</td>
</tr>
<tr>
<td>7.</td>
<td>O Rh, Rh</td>
<td>A1 rh</td>
<td>0</td>
<td>2</td>
<td>O Rh, rh Recovered</td>
</tr>
<tr>
<td>8.</td>
<td>O Rh, Rh</td>
<td>A1 rh</td>
<td>0</td>
<td>2</td>
<td>A1 Rhi rh Recovered</td>
</tr>
<tr>
<td>9.</td>
<td>O Rh, Rh</td>
<td>A1 rh</td>
<td>0</td>
<td>1</td>
<td>O Rh, rh Recovered</td>
</tr>
<tr>
<td>10.</td>
<td>O Rh, Rh</td>
<td>O rh</td>
<td>32</td>
<td>26</td>
<td>O Rh, rh Died edematous and deeply jaundiced, after 24 hours</td>
</tr>
<tr>
<td>11.</td>
<td>O Rh, Rh</td>
<td>O rh</td>
<td>12</td>
<td>25</td>
<td>O Rh, rh Died on 2nd day</td>
</tr>
<tr>
<td>12.</td>
<td>O Rh, Rh</td>
<td>O rh</td>
<td>42</td>
<td>20</td>
<td>O Rh, rh Recovered</td>
</tr>
<tr>
<td>13.</td>
<td>O Rh, Rh</td>
<td>O rh</td>
<td>36</td>
<td>20</td>
<td>O Rh, rh Recovered</td>
</tr>
<tr>
<td>14.</td>
<td>O Rh, Rh</td>
<td>O rh</td>
<td>7</td>
<td>10*,</td>
<td>O Rh, rh Recovered</td>
</tr>
<tr>
<td>15.</td>
<td>O Rh, Rh</td>
<td>B rh</td>
<td>2</td>
<td>14</td>
<td>B Rh, rh Recovered</td>
</tr>
<tr>
<td>17.</td>
<td>A1 Rhi Rh</td>
<td>O rh</td>
<td>2</td>
<td>8</td>
<td>A1 Rhi rh Recovered</td>
</tr>
<tr>
<td>18.</td>
<td>A1 Rhi Rh</td>
<td>O rh</td>
<td>11</td>
<td>3</td>
<td>A1 Rhi rh Recovered</td>
</tr>
<tr>
<td>19.</td>
<td>A1 Rhi Rh</td>
<td>O rh</td>
<td>2</td>
<td>8</td>
<td>A1 Rhi rh Recovered</td>
</tr>
<tr>
<td>20.</td>
<td>A1 Rhi Rh</td>
<td>O rh</td>
<td>11</td>
<td>3</td>
<td>A1 Rhi rh Recovered</td>
</tr>
</tbody>
</table>

**Clinical Summary:**

*All titrations by conglutination method in albumin-plasma; except cases indicated by asterisks which were done by plasma method.*

**Abbreviations used:**

- I.I. = icterus index
- Ebh. = erythroblastosis
- Bl. = titer by blocking technic

**Clinical Summary:**

transfusion can be evaluated. Unfortunately, no comparable series of cases subjected to other types of treatment, such as simple transfusion therapy, is available for comparison. As we and others have shown elsewhere, the most reliable indication of the severity of the disease is provided by antenatal studies of the Rh antibodies in the maternal serum as well as through studies of the Rh antibodies in the infant’s blood. This is demonstrated in table 34 which summarizes those cases that were studied antenatally.

Before discussing table 34 a few words are necessary concerning the relative roles of the bivalent and univalent antibodies in the pathogenesis of erythroblastosis. Whereas originally our tendency was to ascribe almost equal importance to the two kinds of antibodies, the demonstration that the intact placenta allows blocking antibodies (glutinins or univalent antibodies) to pass across freely while holding back agglutinins (bivalent antibodies) has convinced us that the latter play only a subsidiary role in the disease. In fact, the presence of agglutinins in the maternal serum may be entirely misleading, and in one case seen by us recently with an agglutinin titer of more than 100 units, the Rh positive infant subsequently born showed hardly any evidence of erythroblastosis. On the other hand, we have encountered no case with a significant titer of univalent antibodies in which an entirely normal Rh-positive fetus was subsequently born. Nonetheless, the presence of agglutinins is of some significance since it indicates that the mother has been sensitized so that her serum may well contain univalent antibodies in addition. Unfortunately, agglutinins react equally well in plasma and saline media, so that unless the univalent antibodies contained in the same serum are of significantly higher titer their presence would not be demonstrable with the methods available at the time that our cases were studied. Based on this concept one would expect that the severity of the manifestations in the erythroblastotic baby should depend upon the titer of the univalent antibodies in the maternal serum as well as upon the length of time that they were present antenatally. To demonstrate this, the cases have been arranged according to the titer of maternal univalent antibodies at the last test before delivery. For the reasons just discussed these cases are divided into two groups, depending upon whether or not antibodies were also demonstrated by the saline agglutination method.

As shown in table 34, the severity of the manifestations parallels the titer of univalent antibodies in the maternal serum. The 5 infants who died comprise the 2 with the highest titers in the first group and the 3 with the highest titers in the second group. In case 22, in the second group, the infant was but mildly affected, though the titer of the maternal antibodies was relatively high; in this case, the maternal serum most likely contained agglutinins with only weak accompanying univalent antibodies.

In table 35 are summarized those cases in which antenatal tests had not been

* Utilizing the differences in behavior of univalent and bivalent antibodies, such as the difference in resistance to heat, simple methods have been devised whereby univalent antibodies can be detected despite the presence of strong agglutinins.

† This does not include case 11, because we had no access to the mother of this baby and so could not do our own antibody studies.

32. ERYTHROBLASTOSIS AND EXCHANGE TRANSFUSION

done, because the patients were not seen until the infants had developed obvious manifestations of erythroblastosis. Here again the correlation between the titer of maternal antibodies and the prognosis is apparent, since the only infant that died is the one whose mother had the highest antibody titer.

Observation of the infants treated by exchange transfusion immediately convinced us of the efficacy of the treatment so that we did not feel justified in withholding the treatment from any patient merely in order to set up a control series artificially. Since progress in the technics of demonstrating antibodies has paralleled progress in therapy of the disease, even our own previous series do not constitute adequate controls because of incomplete serologic information. In

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Father's Group and Rh-Hr type</th>
<th>Mother's Group and Rh-Hr type</th>
<th>Titer of Maternal Antibodies (units)</th>
<th>Clinical Summary, see bottom of table Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>A₁ Rh₁ Rh₁</td>
<td>A₁ rh</td>
<td>100 (Bl. 4)</td>
<td>Persistent deep jaundice. Dev. sepsis and died at 1 mo.</td>
</tr>
<tr>
<td>6</td>
<td>O Rh₁ Rh₁</td>
<td>A₁ rh</td>
<td>30 (Bl. 1½)</td>
<td>Recovered</td>
</tr>
<tr>
<td>24</td>
<td>B Rh₁ Rh₁</td>
<td>O rh</td>
<td>0</td>
<td>Recovered</td>
</tr>
<tr>
<td>2</td>
<td>B Rh₁ Rh₁</td>
<td>O rh</td>
<td>10</td>
<td>Recovered</td>
</tr>
<tr>
<td>16</td>
<td>O Rh₁ Rh₁</td>
<td>A₁ rh</td>
<td>30</td>
<td>Recovered</td>
</tr>
<tr>
<td>8</td>
<td>A₁ Rh₁ Rh₁</td>
<td>A₁ rh</td>
<td>30</td>
<td>Recovered</td>
</tr>
<tr>
<td>18</td>
<td>A₁ Rh₁ Rh₁</td>
<td>A₁ rh</td>
<td>12</td>
<td>Recovered</td>
</tr>
<tr>
<td>20</td>
<td>O Rh₁ Rh₁</td>
<td>B rh</td>
<td>1½</td>
<td>Very rapid recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CLINICAL SUMMARY:**

arranging the cases under the headings above, both the serologic findings and the severity of the clinical manifestations were taken into account, and it should be emphasized that in some of the severest cases (cases 2, 4, 7 and 8), the recovery after treatment was so rapid that it differed strikingly from anything experienced before this new type of treatment was instituted. It is true that 7 babies died despite treatment, but the clinical and serologic findings indicate that at least twice as many might have died if treated in the orthodox manner, namely, by multiple small transfusions of Rh-negative blood.

In the infants who responded to treatment the results were particularly gratifying for two reasons: (1) The treatment besides being simple, was efficient, and only a few babies required supplementary treatment. In our opinion, it is simpler to do a single exchange transfusion than to do repeated simple transfusions, aside from the
greater efficacy of the former. In those cases that required supplementary transfusions, either bank blood had been used instead of fresh blood, or double sensitization (to A or B as well as Rh) was present. In some cases an intercurrent complication, unrelated to erythroblastosis, made further transfusions necessary. (2.) All the infants who recovered developed normally, both physically and mentally, without any sequelae of liver or brain damage.

Some critics of the procedure have suggested that the infants who died succumbed to the effects of large amounts of citrate used as an anticoagulant in the transfused blood. Evidence is available that the citrate is rapidly metabolized by the infants who survived and it is clear from the case histories that the infants that did not recover died in spite of, and not because of the treatment. The best disproof of the theory of citrate toxicity is our recent observations in which we were able to save infants by doubling the amount of blood used for the exchange transfusion despite the presence in the maternal serum of antibodies with titers which were uniformly lethal when only 500 cc. of blood were used. There is no doubt that there is some degree of toxicity when the exchange transfusion is done too rapidly and a temporary hypocalcemia results. This is readily counteracted by the cautious administration of calcium gluconate.* If the infants show no hypocalcemic symptoms at the termination of the procedure no delayed action of citrate need be feared and no calcium need be administered. The other possible effect of the citrate, namely, to produce an alkalosis, would be expected to be salutary rather than harmful since an "alkaline" pH may tend to prevent serologic clumping and promote excretion of the products of hemolysis. One infant (case 15) died from pyemia, possibly as a result of infection introduced through the use of bank blood, and this is the only fatality that could conceivably be attributed to the treatment itself.

With regard to the technic of the procedure, the method used by us, besides being simple, is safe. We have had no operative mortality in a series of 40 transfusions performed to date. The use of heparin does not appear to be harmful or dangerous since it causes no tendency to bleed except from damaged or cut blood vessels and the heparin effect is nullified by the time the procedure is completed. Different methods of performing exchange transfusions have been suggested by other workers. With regard to the syringe method of Wallerstein, this does not lend itself to the use of large amounts of blood except perhaps for operators with considerable experience and a high degree of technical skill. Some objections have also been raised to the use of the sagittal sinus as the avenue for withdrawing blood. The ingenious umbilical catheter method of Diamond has been widely used and has been considered by some workers to be simpler than the method described by us. Recently, a modification of Diamond's original method has been devised whereby the catheter is inserted through an incision into the femoral vein at the groin instead of through the umbilical vessels. The theoretic objection to the catheter method may be raised that it is a blind procedure and would appear to be tiring to the operators, since syringes must be continuously used to aspirate as well as to inject the blood. More important the method is somewhat dangerous since we

* This is introduced slowly and always directly through the infusion cannula. It is never injected into the tubing.
know of at least two deaths from air-embolism that have occurred, and others in
which death resulted from thrombosis and from hemorrhage into the peritoneal
cavity. Also, technical failures have occurred even in experienced hands when the
umbilical vessels could not be catheterized. Furthermore, the procedure usually
cannot be carried out after twenty-four hours when the umbilical vessels close up.
On the other hand, in our own series of over 40 exchange transfusions performed by
using the radial artery for bleeding and the saphenous vein for the infusion, we have
not had a single technical failure or operative mortality.

SUMMARY

1. In the authors' technic of exchange transfusion, citrated blood is introduced
into the saphenous vein at the ankle and the infant's blood simultaneously with-
drawn from the radial artery at the wrist, coagulation being prevented by the ad-
ministration of small amounts of heparin. The procedure besides being simple, is
safe, there having been no operative mortality in more than 40 transfusions.
2. The results of exchange transfusion therapy in erythroblastosis in our first
28 cases are presented. Of these 28 cases, 16 were very severe and almost certainly
would have been lethal if left untreated, 6 were of moderate severity, and 6 were
mild. Only 7 of the infants died, and the available data indicate that the mortality
would have been at least twice as high had the usual treatment with simple trans-
fusions been given.
3. Aside from its greater efficacy in reducing mortality, exchange transfusion is
more efficient, so that supplementary treatment is not required as a rule.
4. Fresh blood should be used instead of bank blood because of its greater sur-
vival time and smaller likelihood of introducing infection.
5. All infants who have survived have developed normally both physically and
mentally and have shown no sequelae of liver or brain damage.
6. The most reliable index of the severity of the disease in the erythroblastotic
infant is provided by antenatal titrations of the maternal univalent Rh antibodies,
as well as by tests for the presence of univalent antibodies in the infant's blood.

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