THE TREATMENT OF ERYTHROBLASTOSIS FETALIS BY TRANSFUSION WITH SEDIMENTED RED CELLS

By Samuel Pennell, M.D.

Favorable results in the treatment of erythroblastosis fetalis with the transfusion of sedimented red cells in a series of 18 cases have been sufficiently striking to warrant a detailed report of these results. The recently advocated treatment of erythroblastosis fetalis by means of exchange transfusion reported by Wallerstein,1 2 Diamond,4 11 Wiener3 and others is predicated upon the suppositions that (1) if Rh antibodies, particularly of the incomplete or blocking variety, can be demonstrated in the mother prenatally, the child when born will usually have severe erythroblastic disease; (2) the replacement of the affected infant's blood at birth with normal blood by means of exchange transfusion removes the passively transferred antibodies as well as the child's damaged red cells, thus avoiding hemolysis and arresting the progress of the disease.

In the light of more recent information9 10 13 concerning the immunologic mechanisms in this disease, it appears that these hypotheses upon which treatment by exchange transfusion is based need re-evaluation. Levine,9 Davidsohn8 and others have reported that Rh negative mothers showing high Rh antibody titers prenatally, may give birth to Rh positive infants who do not develop severe erythroblastosis, even though Rh antibodies derived from the mother can be demonstrated, both attached to their red cells (sensitized or "coated" cells) or circulating freely in their plasma. Wiener1 12 and Diamond9 11 have shown that the incomplete or blocking Rh antibodies require an "activator," which is supplied by both human serum and bovine albumen, in order to effectuate agglutination of the red cells. Wiener et al.7 have called this substance "conglutinin." Witebsky et al.13 more recently have demonstrated that this "activator" is diminished to an ineffectual level in the plasma of the newborn infant. The addition of plasma of the newborn to cells coated with blocking antibody (sensitized cells) does not supply the required activator or conglutinin, and the expected agglutination of these cells does not occur. On the contrary, they have shown that adult plasma or serum brings about marked agglutination of the red cells which are coated with the blocking antibody, and these authors conclude that normal adult plasma is "the most suitable diluent for bringing about the agglutination of sensitized red cells from infants with erythroblastosis fetalis." They have shown that the addition of as little as one part of adult plasma to nine parts of baby's cord
serum induced marked visible agglutination of the baby’s cells on the slide. "Thus the transfusion of even 30–50 cc. of adult whole blood into the newborn baby might be sufficient to enhance the in vivo hemolysis of the baby’s sensitized cells."

On the basis of this evidence, Witebsky\textsuperscript{13} believes that the transfusion of erythroblastotic children with adult’s whole blood may be contraindicated because the infused adult plasma might activate the incomplete antibody present in the baby. Wiener et al.,\textsuperscript{7} in order to avoid the effect of conglutinin or this activating substance of adult plasma in exchange transfusion, have diluted the conglutinin by removing half of the plasma and replacing it with saline.

Rosenblatt\textsuperscript{14} reports three instances of fatal erythroblastosis in which treatment was limited to exchange transfusions. The autopsies revealed massive necrosis in the liver of all 3 cases. "The lesions were strikingly different from those ordinarily seen in erythroblastosis fetalis." From these findings he concludes: "In view of the lesions described above, exchange transfusion must be considered an unsafe procedure as given at the present time."

**Materials and Methods**

The 18 cases reported here were studied on the obstetrical service of the Maimonides Hospital from January 1947 to December 1948. They consist of two groups; one group of 11 cases due to Rh incompatibility and another group of 7 cases due to ABO group incompatibility.

All women who register as prospective maternity cases have blood typing and Rh determinations performed at the time of registration. Those found to be Rh negative report at regular intervals during the prenatal period in order that the presence and titer of any anti-Rh agglutinins may be determined. The results of these determinations are filed with the patient’s registration card and when the patient is admitted for delivery, these data go into the chart. In addition, a special slip is attached to the front of the chart which states, “This patient is Rh negative; please notify the laboratory as soon as the baby is born.” All infants born to Rh negative mothers thus come to our attention immediately after birth.

A blood count, blood typing, Rh determination and Coombs antiglobulin test are done as soon as possible, and the procedure which is followed in each instance depends on the clinical condition and the blood findings.

For the determination of the presence of anti-Rh agglutinins each maternal serum is inactivated and then set up with Rh\textsubscript{a}, Rh\textsuperscript{+} and Rh\textsuperscript{O} cells in three series, one for saline agglutinins, one for blocking antibodies and one for incomplete agglutinins. For saline antibodies the cells are suspended in saline and incubated. For the blocking antibody the cells are suspended in saline; after incubation and removal of the supernatent fluid potent anti-Rh\textsubscript{a} serum is added and the tubes are then reincubated. For the incomplete antibodies the cells are suspended in 2.0 per cent bovine albumen; after incubation the tubes are read under the low power, both before and after centrifugation.

If agglutinins are demonstrable by any of the three methods, the strength of these agglutinins is determined by making serial dilutions of the maternal serum in the medium (saline or 2.0 per cent bovine albumen) in which the agglutinins were demonstrated and then incubating the entire series of serum dilutions with cells likewise suspended in the same medium.

The criteria which we have used to determine whether the infant required transfusion therapy are the following:

1. **Jaundice.** The presence of jaundice at birth or the development of jaundice in the first thirty-six hours of life was one of the most important indications that treatment was necessary.

2. **Anemia.** The hemoglobin values for the normal newborn infant on the first day of life are given by Wintrobe\textsuperscript{19} as 19.5 Gm. per cent ± 1.0. Since in our hospital the values obtained in 10 normal newborn infants on the first day of life averaged 19.8 Gm. per cent, we consider 20 Gm. per cent of the hemoglobin to be our normal standard. Any erythroblastotic infant who has 15 Gm. per cent of hemoglobin or less within thirty-six hours of birth is considered anemic and therefore in need of a transfusion.
The red cell values in normal newborn infants are correspondingly high. In cases of erythroblastosis, a falling hemoglobin is accompanied by a corresponding fall in red cell values, so that along with the level of 15 Gm. per cent of hemoglobin we consider 4.0 million red cells per cu. mm. a critical level. These values for hemoglobin and red cells which we consider critical are about 70 per cent of our criteria for normal newborn infants.

3. Erythroblastosis. The presence of an abnormal number of nucleated red cells in the peripheral blood is an important sign in this disease. The upper limit of normal for nucleated red cells of the newborn infant is given by Wintrobe as 2.00 per cu. mm. In most of our cases the values were very much higher than this, but we believe that the presence of nucleated red cells, although a valuable diagnostic sign, must be considered in combination with other data, such as anemia and jaundice, and should not be used as an indication per se for treatment.

4. Agglutinins. Another important symptom is the presence of anti-Rh agglutinins in the mother’s serum combined with the demonstration that the infant is Rh positive or has blocking antibodies attached to its red cells (Coombs antiglobulin test). If the erythroblastosis appears to be due to a discrepancy of the ABO blood groups between mother and child, an unusually high titer of anti-A or anti-B agglutinins should be demonstrable in the mother’s serum.

5. History. A history of previous infants with erythroblastosis born to the mother or a history of previous sensitization of an Rh negative mother by an Rh positive transfusion are important considerations in evaluating the need for treating the newborn who has erythroblastosis.

The above criteria which we have used in determining whether or not the child requires transfusion are fairly similar to those employed as a guide by Diamond, and Mollison and Cutbush. Diamond states: “We assume that the presence of these clinical signs (anemia, jaundice, edema, splenomegaly, and hepatomegaly) with antibodies in the mother’s circulation implies the need for immediate replacement transfusion.”

Mollison and Cutbush believe that infants whose hemoglobin values fall to between 8.0 and 14.5 Gm. per cent are those who require treatment, those with hemoglobin values above 14.5 Gm. per cent recover without any treatment and those with hemoglobin values below 8 Gm. per cent do not survive. They also consider the presence of erythroblastemia an important sign in evaluating the severity of the disease, since all of their cases which required treatment showed erythroblasts in the peripheral blood.

Transfusion Technic

All transfusions in our institution are given with bank blood. Since several bottles of each type of blood, including Type O Rh negative, are kept constantly on hand, the blood remains in the icebox long enough for the red cells to sediment thoroughly. The bottles used are of the “Baxter” type and have a glass tube which is attached to the stopper (fig. 1). This glass tube extends from the stopper to within ½ inch of the bottom of the bottle and is used as an airway. When the blood has settled, this glass airway extends down well within the layer of red cells at the bottom. The bottle of blood to be used is carried carefully so as not to disturb the sedimented red cells. The rubber stopper of the blood bottle is marked with two round depressions. The larger of these indicates the point at which the glass drip is usually inserted. The smaller overlies the glass airway. When the transfusionist is ready to administer the cells, the vacuum in the bottle is broken by thrusting a large gage needle (15-17 gage) through the larger depression in the
stopper. (The vacuum must not be broken by thrusting the needle through the smaller depression, for the air rushing in through the airway would come up through the layer of red cells and stir it up.) When the vacuum has been broken, another large gage needle (preferably 15 gage) is thrust through the smaller depression of the rubber stopper and into the airway. The red cells from the bottom of the bottle are then drawn up via this needle and the airway into which it extends. A 50 cc. syringe is connected either directly to the needle in the airway or to a three-way stopcock arrangement.

If care is taken not to run any of the cells back, 60 cc. or more of the sedimented cells can be readily withdrawn without disruption of the line of demarcation between the cells and plasma. When the desired amount of cells has been drawn into the syringe the stopcock is turned, and the cells can then be administered either by way of a scalp vein or through an incision into a cubital or ankle vein. We have found that in most cases the newborn infants have temporal veins which can be entered with a 22 gage needle. The sedimented cells can readily be forced through this size needle and it takes no more than fifteen or twenty minutes to administer 50–60 cc. of cells.

To our knowledge, red cells practically free of plasma have not been transfused in the manner above described. Wiener and Sonn describe the transfusion of washed packed red cells to an infant with erythroblastosis from the child’s Rh negative mother. They state that if the plasma which contains the anti-Rh agglutinins is completely removed and the red cells washed, it is then perfectly safe to transfuse these red cells to the affected Rh positive infant. The preparation of such washed cells requires equipment and technical facilities not generally available, and in addition introduces a fair possibility of contamination due to the handling of the blood involved.

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**Fig. 1.** — Apparatus used in transfusion
SAMUEL PENNELL

It has seldom been necessary to give over one syringe-full (50-60 cc.) at one treatment. This amount causes the hemoglobin to rise anywhere from 2.7 Gm. to

Table 1.—Summary of Data in Wallerstein’s Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Onset of Jaundice</th>
<th>Hg. Grams. %</th>
<th>R.B.C. Mill. cu. mm.</th>
<th>Nuc. R.B.C. cu.mm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>17.5</td>
<td>4.6</td>
<td>20,000</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>14.5</td>
<td>3.9</td>
<td>30,000</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>13.0</td>
<td>3.9</td>
<td>26,000</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>14.0</td>
<td>3.8</td>
<td>Not stated</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>Not given</td>
<td>3.9</td>
<td>Many</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>12.0</td>
<td>Not given</td>
<td>31,000</td>
</tr>
<tr>
<td>7</td>
<td>Not given</td>
<td>23.0</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>8.5</td>
<td>1.9</td>
<td>49,000 (Died)</td>
</tr>
<tr>
<td>9</td>
<td>24</td>
<td>14.0</td>
<td>4.1</td>
<td>22,000 (Died)</td>
</tr>
</tbody>
</table>

Table 2.—Summary of Data in Wiener’s Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Onset of Jaundice</th>
<th>Hg in Gm. %</th>
<th>R.B.C. in Mill. cu.mm.</th>
<th>Nucleated R.B.C.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recovered cases.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>At birth</td>
<td>8.8</td>
<td>3.7</td>
<td>48,000 Cu.mm.</td>
</tr>
<tr>
<td>2</td>
<td>Not given</td>
<td>13.6</td>
<td>Not given</td>
<td>12 per 100 WBC.</td>
</tr>
<tr>
<td>3</td>
<td>After Exch.</td>
<td>15.5</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>4</td>
<td>Within 24 Hrs.</td>
<td>11.5</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>5</td>
<td>After Exch.</td>
<td>Not given</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>6</td>
<td>Within 36 Hrs.</td>
<td>11.7</td>
<td>2.9</td>
<td>7 per 100</td>
</tr>
<tr>
<td>7</td>
<td>After Exch.</td>
<td>17.4</td>
<td>6.0</td>
<td>Not given</td>
</tr>
<tr>
<td>8</td>
<td>Within 24 Hrs.</td>
<td>14.5</td>
<td>4.7</td>
<td>4,000 Cu.mm.</td>
</tr>
<tr>
<td>9</td>
<td>At birth</td>
<td>8.1</td>
<td>Not given</td>
<td>15 per H.P. Field</td>
</tr>
<tr>
<td>10</td>
<td>None</td>
<td>16.0</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>11</td>
<td>Within 24 Hrs.</td>
<td>12.3</td>
<td>3.4</td>
<td>3 per 100 WBC.</td>
</tr>
<tr>
<td>12</td>
<td>Within 24 Hrs.</td>
<td>13.5</td>
<td>3.4</td>
<td>5 per 100 WBC.</td>
</tr>
<tr>
<td>13</td>
<td>None</td>
<td>17.4</td>
<td>4.3</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>None</td>
<td>18.0</td>
<td>5.78</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>Within 18 Hrs.</td>
<td>10.2</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>16</td>
<td>Within 24 Hrs.</td>
<td>18.0</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>17</td>
<td>Within 12 Hrs.</td>
<td>12.9</td>
<td>4.33</td>
<td>Not given</td>
</tr>
<tr>
<td>18</td>
<td>None</td>
<td>12.7</td>
<td>3.8</td>
<td>10 per 100 WBC.</td>
</tr>
<tr>
<td></td>
<td>Fatal cases.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>After Exch.</td>
<td>11.7</td>
<td>2.62</td>
<td>Not given</td>
</tr>
<tr>
<td>20</td>
<td>Not given</td>
<td>5.8</td>
<td>1.5</td>
<td>16,000 per Cu mm.</td>
</tr>
<tr>
<td>21</td>
<td>Fourth day</td>
<td>Not given</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>22</td>
<td>At birth deepened after exchange.</td>
<td>9.0</td>
<td>2.1</td>
<td>164 per 100 WBC.</td>
</tr>
<tr>
<td>23</td>
<td>After Exch.</td>
<td>4.3</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>24</td>
<td>After Exch.</td>
<td>5.8</td>
<td>1.25</td>
<td>Not given</td>
</tr>
</tbody>
</table>

8 Gm. (this rise in hemoglobin usually puts the child into the safe range, above 14.5 Gm.). Hemoglobin and red cell values are determined daily. and if the hemo-
globin again falls below 15.0 Gm. another transfusion of 50 or 60 cc. of cells is
given. We have seldom found it necessary to give more than this amount.

Comparison of present series with cases reported in the literature. Although a number
of articles concerning the treatment of erythroblastosis fetalis by means of ex-
change transfusions have recently appeared, only two authors, Wallerstein and
Wiener, give the data of their cases in sufficient detail for use in comparison as
to severity of the disease, criteria for treatment and results obtained. Wallerstein
reports 9 cases in detail, and Wiener 28 cases, of which 14 are reported in detail.
All the other authors state the number of cases they have treated and give detailed
data in only one or two. A summary of the data of Wallerstein's cases (table 1)
and Wiener's cases (table 2) has been prepared and is included for purposes of
comparison.

Results and Analysis of Data

The data of our cases is presented in tables 3, 4 and 5. Table 3 is a summary of
the 19 cases due to Rh incompatibility which recovered. Table 4 is a summary of
the 6 cases due to ABO group incompatibility which recovered and table 5 is a
summary of the fatal cases. In 15 cases only one transfusion was required, in 8
cases two were given, and in 2 cases three were found necessary.

Cases due to Rh Incompatibility

All 21 cases in this group showed early jaundice; 16 developed jaundice within
the first twelve hours after birth, 4 within twenty-four hours and 1 within thirty-
six hours.

Anemia. As stated above, we have found the mean normal values for hemoglobin
and red cells in the newborn to be 20 Gm. per cent and 6.1 millions per cu. mm.
respectively. In our surviving cases the hemoglobin values before transfusion were
as follows: In 1 case 6.5 Gm. per cent, in 2 cases 9.5 Gm. per cent, in 8 cases 11.5-
12.5 Gm. per cent, in 10 cases 13.0-14.5 Gm. per cent and in 4 cases 15.5-16.0 Gm.
per cent.

The 4 cases which were treated when the hemoglobin values were between 15.5
and 16.0 Gm. per cent all had the disease in severe form. In addition, infants 5 and
13 were siblings born a year apart to a mother who had a high anti-Rh agglutinin
titer in her blood prenatally in both pregnancies and had lost two children in
previous pregnancies due to erythroblastosis fetalis. Because of this history the
infants were transfused while the hemoglobin was still above 15 Gm.

Levine and Waller reported a series of cases of erythroblastosis in the first born
in which Rh negative women, who had been sensitized by transfusions with Rh
positive blood some time in their past history, subsequently gave birth to erythro-
blastotic children at the termination of their first pregnancy.

The mother of Case 12, who was Rh negative, had been sensitized in her youth
by a transfusion, probably of Rh positive blood; as a result of this she had lost her
first baby due to erythroblastosis. This was her second pregnancy and she had a
high anti-Rh agglutinin titer in her serum prenatally. In this case a transfusion
was given when the hemoglobin was still 15.5 Gm. per cent.
### Table 3.—Erythroblastosis Fetalis—Recovered. Due to Rh Incompatibility

<table>
<thead>
<tr>
<th>Case</th>
<th>Obstetrical history</th>
<th>Mother Blood group*</th>
<th>Infant Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Saline In-complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood group</td>
<td>Onset of jaundice</td>
</tr>
<tr>
<td>1</td>
<td>Second Preg. 1st child alive and well.</td>
<td>O — 1-64 O</td>
<td>Within 9.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 12 hrs. 13.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 19.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 14.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 17.5</td>
</tr>
<tr>
<td>2</td>
<td>Second preg. 1st child nor.</td>
<td>O — 1-8 O</td>
<td>Within 16.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 24 hrs. 12.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 17.5</td>
</tr>
<tr>
<td>3</td>
<td>Fourth preg. 1st three alive and well. No history of erythroblastosis.</td>
<td>B 1-4 1-16 B</td>
<td>Within 12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 12 hrs. 15.5</td>
</tr>
<tr>
<td>4</td>
<td>Third pregnancy, 1st, abortion. 2nd, miscarriage</td>
<td>O — 1-8 A</td>
<td>Within 17.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 12 hrs. 14.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 17.0</td>
</tr>
<tr>
<td>5</td>
<td>Fourth pregnancy, 1st marriage, 2nd child nor., 2nd marriage, 1st child died of erythroblastosis</td>
<td>O — 1-8 O</td>
<td>Within 16.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 6 hrs. 16.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 22.5</td>
</tr>
<tr>
<td>6</td>
<td>Fourth pregnancy, 1st nor. child, 2nd miscarriage, 3rd, nor. child.</td>
<td>O — 1-32 O</td>
<td>Within 9.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 6 hrs. 16.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 13.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 19.0</td>
</tr>
<tr>
<td>7</td>
<td>Second Preg. 1st born nor. died 6 mos. pn.</td>
<td>A 1-4 1-64 A</td>
<td>Within 12.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 6 hrs. 19.0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>3 14.5</td>
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<td></td>
<td></td>
<td></td>
<td>4 19.0</td>
</tr>
<tr>
<td>8</td>
<td>Third preg. 1st child nor., 2nd child erythroblastosis with recovery.</td>
<td>O — 1-32 O</td>
<td>Within 22.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 24 hrs. 12.5</td>
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<td>8 15.5</td>
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<td></td>
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<td>20 10.5</td>
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<td></td>
<td></td>
<td></td>
<td>22 13.5</td>
</tr>
<tr>
<td>9</td>
<td>Second preg. 1st. child alive and well.</td>
<td>O — 1-16 A</td>
<td>Within 14.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 6 hrs. 13.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 16.0</td>
</tr>
<tr>
<td>10</td>
<td>Second preg. 1st child no trouble at birth, alive and well</td>
<td>A — 1-256 A</td>
<td>Within 13.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 6 hrs. 19.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 16.0</td>
</tr>
<tr>
<td>11</td>
<td>1st pregnancy. No history of abortion or previous transfusion could be obtained</td>
<td>A — 1-128 A</td>
<td>Within 17.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 12 hrs. 14.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 17.5</td>
</tr>
<tr>
<td>12</td>
<td>2nd pregnancy. 1st child died of erythroblastosis. Pt. had transfusion in her early youth, probably Rh+ and was sensitized by it</td>
<td>O — 1-256 O</td>
<td>Within 17.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 6 hrs. 15.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 16.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 25.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20 15.0</td>
</tr>
</tbody>
</table>
The table gives only the data which we considered pertinent. Daily blood counts were done in all cases. Not all the blood counts appear in the chart. Only the counts which are significant and the age at which they were done are shown.

\* All mothers Rh negative.
\dagger All infants Rh positive.
\ddagger Rh negative whole blood transfused.
\$ Condition good on discharge in all cases. Case 18 premature; kept in nursery until three weeks old.

The infant in Case 13 was severely jaundiced and in generally poor condition at birth. It was transfused when the hemoglobin was still 16 Gm. per cent but in spite of this, subsequent blood counts indicated severe hemolytic disease (table 3). Even though the first transfusion had raised its hemoglobin to 23.0 Gm. per cent and 5.9 million red cells per cu. mm. on the second day of life, the hemolytic process was so severe that by the sixth day the hemoglobin had fallen to 14.0 Gm. per
cent and the red count to 3.6 million per cu. mm. This child required three transfusions before it was discharged from the hospital.

The above 4 cases all had severe erythroblastosis fetalis and their case histories contain all the necessary clinical, hematologic and serologic criteria which would have surely made them candidates for exchange transfusion at birth by those who employ this procedure in the treatment of erythroblastosis fetalis.

Case 2.1 deserves particular mention. This 2.5 pound premature twin (the other twin was stillborn) was jaundiced at birth and the mother showed a high anti-Rh agglutinin titer; the red cells were coated as indicated by a positive Coombs test. Twenty-four hours after birth the child’s hemoglobin had fallen to 12 Gm. per cent from an original high of 18.5 Gm. per cent and the jaundice had deepened. Only 30 cc. of sedimented red cells were transfused because of this infant’s small size, and this amount was sufficient to raise the hemoglobin to 19.0 Gm. per cent and the red cells to 5.9 million per cu. mm. No further transfusions were necessary. The child was kept in an incubator in the “premature” nursery and is at present six weeks old and progressing satisfactorily.

In our series among the infants who recovered, none had a hemoglobin value before treatment higher than 16.0 Gm. per cent. In Wallerstein’s series, 2 of the infants who recovered had, before they were treated with exchange transfusion, hemoglobin values higher than this, one having 17.5 Gm. per cent and the other 23.0 Gm. per cent. In Wiener’s series, 4 cases had hemoglobin values before exchange transfusion higher than any in our series, 2 having had 17.4 Gm. per cent and 2 having had 18.0 Gm. per cent.

Erythroblastosis. All 21 cases showed nucleated red cells in their peripheral blood, at least in the first blood count. The number ranged from a high of 200,000 per cu. mm. to a low of 16 per cu. mm. We feel that erythroblastosis when present is corroborative evidence of hemolytic disease, but that its absence does not contraindicate transfusion therapy if there is a rapidly developing anemia.

In 5 cases (4, 8, 9, 15 and 19) there is not only an Rh incompatibility, but an ABO group incompatibility as well. The serum of all mothers in these cases showed anti-Rh agglutinins. Titration of the anti-A and anti-B agglutinins in the maternal serum showed the titer to be within normal limits (below 1:80). The fact that only the Rh agglutinogen immunizes when a double incompatibility (Rh and ABO) occurs has been noted many times previously, and Levine⁵ states that there does not seem to be any logical explanation why they both do not immunize when there is a double incompatibility.

Etiology. In the above 21 cases the disease was due to an incompatibility of the Rh factor, the mothers being Rh negative and the infants Rh positive. The serum of all of these mothers was shown to contain anti-Rh agglutinins. In 18 infants in this group of 21, the Coombs test was positive when performed on the infants’ washed red cells.

Cases due to ABO Group Incompatibility

In 7 of our 28 cases the disease appeared to be due to an incompatibility of the ABO blood groups between mother and child. All mothers in this group showed a significant rise in either anti-A or anti-B agglutinin titer (table 5), apparently in
response to the infant's A or B cells which had found their way into the maternal circulation during the pregnancy.

**Rise in hemoglobin.** The average rise in hemoglobin which we obtained following the transfusion of 50–60 cc. of sedimented red cells was 5 Gm. per cent, the smallest rise being 2.7 Gm. per cent and the greatest 8 Gm. per cent. In most cases the ad-

### Table 4. Erythroblastosis Due to ABO Incompatibility—Recovered

<table>
<thead>
<tr>
<th>Case</th>
<th>Mother</th>
<th>Infant</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetrical history</td>
<td>Agglutinins</td>
<td>Onset of jaundice</td>
<td>Nucl. R.B.C. (millions)</td>
</tr>
<tr>
<td>1</td>
<td>2nd pregnancy. 1st child alive and well</td>
<td>Anti-A 1-32 Anti-B 1-512</td>
<td>1 2 Within 20.5</td>
</tr>
<tr>
<td>2</td>
<td>2nd pregnancy. 1st child alive and well. No history of severe jaundice</td>
<td>Anti-A 1-236 Anti-B 1-64</td>
<td>1 Within 14.0</td>
</tr>
<tr>
<td>3</td>
<td>1st pregnancy. No miscarriages or abortions</td>
<td>Anti-A 1-236 Anti-B 1-64</td>
<td>1 birth 13.5</td>
</tr>
<tr>
<td>4</td>
<td>1st pregnancy</td>
<td>Anti-A 1-32 Anti-B 1-512</td>
<td>1 Within 20.5</td>
</tr>
<tr>
<td>5</td>
<td>1st pregnancy</td>
<td>Anti-A 1-32 Anti-B 1-512</td>
<td>1 At 15.5</td>
</tr>
<tr>
<td>6</td>
<td>2nd pregnancy. 1st child alive and well</td>
<td>Anti-A 1-32 Anti-B 1-512</td>
<td>1 Within 20.5</td>
</tr>
</tbody>
</table>

The chart shows only the data which we considered pertinent. Although daily blood counts were done in all cases, the chart shows only the counts which are significant and the age at which they were done.

* All mothers, blood group O, Rh positive, except Case 3 (group O, Rh negative).
* All infants, blood group A, Rh positive, except Case 3 (group A, Rh negative).
* Condition of all infants good on discharge.

ministration of 50–60 cc. of sedimented cells brought the infants' hemoglobin to 14.5 Gm. per cent or above, a level at which it was considered safe to observe the infant until a further fall in hemoglobin and red cell values indicated the need for another transfusion.

### Fatal Cases

**Case 26.** The mother was Group AB, Rh negative and showed incomplete (blocking) anti-Rh agglutinins in her serum up to a dilution of 1:512. The infant was Group A, Rh positive. At birth there was...
Infant
Mother
Case
No.
Obstetrical history
Blood
factor
Rh
groups
Agglutinins
Clinical description
Infant

26 2nd pregnancy. 1st All
child normal at birth.
Died at 3 wks. of age
pneumonia.
Nez
Incomplete
1-312
type
Jaundiced at birth.
Generalized petechiosis.
Bleeding from
nose and mouth.
Liver enlarged to
iliac crest. Spleen
2 fingers below
costal margin.
1 6.0
1.2 58,000
75 cc. cells
75 cc.
RBC.
en

27 1st pregnancy. No 0
history of miscarriages
or abortions.
Pos
Anti A
1-1800
Marked jaundice at
birth. Generalized
edema. Generalized
petechiosis. Bleeding
from mouth and nose.
Liver enlarged to
iliac crest. Spleen
enlarged two fingers
below costal margin.
1 19.0 4.2
2,400
50 cc. Cells.

28 3rd pregnancy. 1st AB
miscarriage at 2 mos.
2nd died shortly after
birth and was jaundiced.
Nez
Incomplete
1-256
type
Jaundiced at birth.
Vernix deep
yellow. Marked
palor as well as
cyanosis. Scrotum
and legs edematous.
Respiratory
difficulty from
birth. Rapid
grunting. Expectorated
brown sputum.
1 9.5
40,000
75 cc. Cells
1.9 10,000
25 cc.
RBC.
en

* All infants blood groups A, Rh positive. All infants died. Autopsy findings:


Case 27: All organs bile tinged. Liver very large, 200 Gm. spleen very large, 100 Gm. No necrosis of liver. Microscopic: Practically all the liver tissue was replaced by hematopoetic foci.

Case 28: Heart enlarged. Lungs engorged: only the edge of one lobe was pink and aerated. Liver very large, 210 Gm. Spleen very large, 100 Gm. No necrosis of liver. All organs bile tinged.

Autopsy revealed the findings typical of severe erythroblastosis fetalis. All organs were jaundiced, the liver and spleen were very large and there was generalized petechiosis of the serosa of the liver, spleen, intestines and peritoneum. The liver showed no massive necrosis on cut surface. Microscopic examination showed extensive replacement of liver tissue by centers of hemopoiesis.

Case 27. The cause of the erythroblastosis in this case was an incompatibility of the ABO blood groups. The mother was type O, Rh positive and had an anti-A agglutinin titer of 1:1800 and anti-B agglutinin titer of 1:80. No agglutinins could be demonstrated in the mother's serum either against O, Rh positive or O, Rh negative cells suspended in saline or plasma-albumin. The infant was type A, Rh positive, and at birth showed deep jaundice, generalized edema, generalized petechiosis, bleeding from
the mouth and nose, enlargement of the liver to the iliac crest and of the spleen to 2 fingerbreadths below the costal margin. In spite of the severe clinical signs, the hemoglobin was 19.0 Gm. per cent, the R.B.C. 4.2 million per cu. mm. and there were 2400 nucleated red cells per cu. mm. A transfusion of 50 cc. of sedimented red cells of the type O, Rh positive blood was given, but the child died shortly after this procedure was completed. Autopsy showed all the organs to be bile-tinged. The liver and spleen were very large, weighing 100 and 100 Gm. respectively. The liver on cut surface showed no massive necrosis. Microscopic examination revealed that practically all liver tissue was replaced by extensive foci of hematopoeisis.

It is generally considered that erythroblastosis fetalis due to ABO blood group incompatibility is a mild disease. This case illustrates, however, that erythroblastosis of this etiology can be severe enough to cause death. This child presented the most marked clinical signs of erythroblastosis of any of our cases.

Two reports of erythroblastosis due to ABO group incompatibility have appeared in the recent literature. Mitchel et al.23 report 3 fatal cases and Tisdall et al.24 report 2 cases which recovered after transfusion.

Case 28. The mother of this child was Group AB, Rh negative and incomplete (blocking) anti-Rh agglutinins could be demonstrated in her serum up to a dilution of 1:128. The infant was Group A, Rh positive and showed jaundice as well as a deeply stained vernix at birth. There was, in addition, cyanosis and respiratory difficulty, the breathing being rapid and grunting in character. A brownish mucoid discharge drooled from the corners of the mouth, and the scrotum and legs were edematous. The hemoglobin at birth was 9.5 Gm. per cent, the R.B.C. was 1.9 million per cu. mm. and there were 40,000 nucleated red cells per cu. mm. The child was placed in an oxygen tent immediately, and 75 cc. of sedimented red cells type A, Rh negative was transfused within one hour of birth. The hemoglobin rose to 16.5 Gm. per cent and the R.B.C. to 4.0 million per cu. mm. The color improved but respiratory difficulty continued, the child becoming cyanotic whenever it was removed from the oxygen tent. The following day another transfusion of 50 cc. of sedimented red cells was given and the hemoglobin rose further to 17 Gm. per cent and the R.B.C. to 4.5 millions per cu. mm. The respiratory difficulty and the brownish secretion from the mouth continued, however, and the child died while in the oxygen tent on the third day of life.

At autopsy the lungs showed general engorgement, only the edge of one lobe being pink and aerated. Both the liver and spleen were markedly enlarged, the liver weighing 210 Gm. and the spleen 100 Gm. All the organs were bile-tinged and the liver on cut surface showed no areas of necrosis.

Comparison of Present Series with Cases in the Literature

A comparison as to the severity of Wallerstein’s and Wiener’s cases with our own reveals the following:

Onset of jaundice. In Wallerstein’s2 series, only one of the 9 cases showed jaundice within twelve hours of birth. In Wiener’s21 series only 3 of the 28 cases showed jaundice within twelve hours of birth, while in our own series 18 of the 28 cases showed jaundice within twelve hours after birth. In 6 of Wiener’s cases the jaundice was not present before the exchange transfusion, but appeared only after the exchange procedure had been performed and theoretically up to 98 per cent of the treated infant’s blood had been washed out. In a seventh case, the jaundice was present before the exchange transfusion, but deepened after the exchange of blood had been carried out.

Anemia. The average hemoglobin values before treatment of Wallerstein’s cases was 14.6 Gm. per cent, of Wiener’s cases 13.0 Gm. per cent and of our own series 13.7 Gm. per cent. It is interesting to note that in Wiener’s series, 4 of the cases treated with exchange transfusion were treated on the basis of history alone. They
showed no jaundice or erythroblastosis at any time, and 3 of them (Cases 10, 13 and 14) had initially high hemoglobin and red cell values.

Many of our cases which showed jaundice and anemia at birth received transfusions of sedimented red cells within two or three hours. A substantial rise in hemoglobin and red cell values were obtained, but in spite of this rise induced by transfusion, a sharp fall in hemoglobin and red cells occurred within twenty-four to forty-eight hours, indicating that severe hemolysis of the infant's cells was taking place. This phenomenon can be seen especially in the cases which required two or more transfusions (1, 6, 7, 8, 12, 13, 14, 17 and 19, table 3). On this basis, we believe that if these infants had not been treated promptly after birth, and that if the treatment had been delayed for twenty-four hours or more, the hemoglobin and red cell values would have been much lower and perhaps our treatment might not have been effective.

**Discussion**

It has long been recognized that erythroblastosis fetalis is a hemolytic disease and that its treatment consists primarily of the transfusion of blood to replace that which is destroyed by the hemolytic process in the infant. With the discovery of the Rh factor and the development of knowledge in this field, it became clear that the erythroblastotic infant's red cells which contained agglutinogens (Rh and Hr) were being destroyed by hemolysis due to the influence of anti-Rh and Hr agglutinins derived from the mother. It was first pointed out by Levine et al., and has been generally accepted, that any blood transfused to such infants should have red cells of the infant's own blood group but should not contain any agglutinogens which could react with the agglutinins responsible for the hemolysis, i.e., Rh negative cells. When it was subsequently demonstrated that erythroblastosis fetalis can also occur because of A and B agglutinogen incompatibility between mother and child, it became the accepted procedure to transfuse such erythroblastic infants with type O blood. Since type O cells contain neither A nor B agglutinogens they could not be destroyed by the corresponding agglutinins.

Simple transfusion of whole blood often proved inadequate, partly because the quantity which could be given safely to the newborn infant was frequently too small to overcome the severe anemia, and partly, no doubt, because of the harmful effect of the adult plasma which was of necessity transfused as part of this whole blood. The advent of exchange transfusion seemed at first to offer the solution to the problem. The technic generally employed is to administer 500-1,000 cc. of Rh negative blood to the infant while a similar amount is allowed to flow or is withdrawn from the infant during the procedure. This produces in the infant an admixture of infant's and transfused blood. Since the volume of the transfused blood is two to four times the entire volume of the blood of the infant, the procedure is theoretically supposed to replace 85 to 98 per cent of the infant's blood. Exchange transfusion has proved difficult and required specially trained highly skilled teams, and the mortality instead of being reduced to a minimum has remained high. It was subsequently reported by Rosenblatt that infants who
succumbed after exchange transfusion showed at autopsy massive liver necrosis and other pathologic changes quite different from any lesions previously described in erythroblastosis. He stated that these destructive lesions might be due to the large amount of sodium citrate necessarily administered with 500-1,000 cc. of blood, to the large amounts of calcium gluconate given to counteract the effects of the sodium citrate or to the speed with which exchange transfusion is carried out.

There is another factor to be considered, however, which might be responsible for the destructive lesions described by Rosenblatt. This is the possibility that the large amount of adult plasma given during exchange transfusion (55 per cent of the blood volume) causes massive intravascular hemolysis of the infant’s red cells (Witebsky) before they can be removed from the infant’s circulation in the exchange of blood. Such a concept would explain the observation reported both by Wallerstein and Wiener that severe jaundice sometimes develops twenty-four hours after exchange transfusion, even though no jaundice has been evident before. Since the exchange transfusion supposedly removes 85 to 98 per cent of the infant’s red cells and replaces them with cells which should not hemolyze, the development of severe jaundice after exchange transfusion can be explained only by assuming that a large proportion of the infant’s sensitized cells, instead of being removed during the exchange, undergo massive hemolysis due to the “activating” effect of the large amount of adult plasma which enters the infant’s blood stream.

The transfusion of sedimented red cells to the erythroblastotic infant, as reported in this paper, appears to have the following advantages. The severe anemia which is present is overcome by a comparatively small volume (50-60 cc.) of cells, which cannot overburden the infant’s circulatory system. The procedure for administering the sedimented cells is simple, can be carried out by way of a scalp vein, takes only fifteen to twenty minutes, does not require any special equipment or specially trained transfusion teams and is available wherever there is a blood bank. Furthermore it eliminates the administration to the infant of large amounts of extraneous substances such as sodium citrate, heparin and calcium gluconate which are employed in exchange transfusion. The amount of adult plasma which the sedimented red cells contain is shown by hematocrit studies to be about 5 per cent. Thus, a child who is given 60 cc. of sedimented cells receives only about 3 cc. of adult plasma. This amount of plasma is probably much too small to cause activation of any agglutinins which might be present in the infant, and the amount of sodium citrate which it contains is so minute that it cannot possibly cause harm.

The fact that the infant’s coated cells are allowed to remain, no attempt being made to remove them as in exchange transfusion, seems to be of no consequence, in our series at least, for our follow-up shows that of the 25 cases which survived, 24 are alive and well and only one (Case 1, table 4), an OA discrepancy case, appeared to be abnormal and died at the age of 22 months.

It is of course difficult to draw conclusions from so small a series of cases. However, our series compares favorably as to severity with the cases available for comparison in the literature which were treated by exchange transfusion. Wallerstein reports his series of 27 cases with a mortality of 22 per cent, Wiener reports a series of 28 cases with a mortality of 25 per cent, and Diamond a series of 85 cases
with a gross mortality of 2.4 per cent and a corrected mortality of 1.5 per cent. Our series of 28 consecutively occurring cases with 3 deaths shows a mortality of 10.7 per cent.

At present the mainstay of therapy in erythroblastosis fetalis consists of the transfusion of blood to the affected infant by one method or another.

**Summary**

1. A method is described for the treatment of patients with erythroblastosis fetalis by the transfusion of compatible sedimented red cells from bank blood.

2. The case histories of 28 patients with erythroblastosis fetalis, treated by this method, have been analyzed. Three, or 10.7 per cent, of the patients died. This mortality rate compares favorably with other reports in which exchange transfusion was the therapeutic procedure.

3. The transfusion of sedimented red cells in 50–60 cc. amounts is sufficient to cause an adequate rise in the hemoglobin values with a minimum of load on the infant's circulation.

4. This method, in contrast to that of exchange transfusion, has the advantage of reducing the administration of plasma to a minimum, thereby preventing further hemolysis of the infant's red cells by enhancing the agglutinin titer. In addition, excessive amounts of extraneous substances such as sodium citrate are not given.

**References**


12.2.

TRANSFUSION IN ERYTHROBLASTOSIS FETALIS

THE TREATMENT OF ERYTHROBLASTOSIS FETALIS BY TRANSFUSION WITH SEDIMENTED RED CELLS

SAMUEL PENNELL