THE TREATMENT OF ERYTHROBLASTOSIS FETALIS
BY SUBSTITUTION TRANSFUSION

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The treatment of erythroblastosis fetalis by the substitution of Rh negative blood for the baby's original Rh positive erythrocytes in a simultaneous exsanguination-transfusion procedure was suggested because:

1. Other methods of transfusion therapy proved only partially effective. Even before the theory of isoimmunization of the mother by an antigen in the fetal red blood cells was postulated by Levine, and the antigen identified as similar to one experimentally produced by Landsteiner and Wiener, blood transfusion was the treatment of choice. Blood was given by subcutaneous, intramuscular or intraperitoneal injection, but the repeated intravenous administration was considered best. Although it was noted that results following transfusion were somewhat better if nonfamily donors were used, the father usually acted as the source of blood. It is now known that father's blood is entirely unsuitable because it always carries the same antigen as the blood of the affected infant. This was also true in 85 per cent of the cases in which professional donors were chosen at random. Many of the infants appeared to suffer the equivalent of a transfusion reaction with increasing jaundice, toxicity and fever, and 80 per cent of these infants died irrespective of the form of therapy. When Rh negative blood was used to replace the infant's hemolyzed erythrocytes, the untoward reactions did not occur and anemia was swiftly brought under control. Nevertheless, from 35-50 per cent of these infants still died. Autopsy usually showed findings identical to those previously reported, even though anemia and transfusion reactions were no longer factors. The reasons are obvious when one recalls that all or nearly all of the baby's Rh positive blood would frequently be destroyed, and the infant actually became temporarily Rh negative to the test.

2. Postmortem examination of the infants who died despite repeated transfusion with Rh negative blood revealed that death was usually due to overwhelming toxicity induced by liver insufficiency. It is probable that kernicterus occurs only after such liver damage. The role of the liver in the pathogenesis of erythroblastosis has been schematically shown by Davidsohn and his description clearly illustrated the reasons why former transfusion methods were so often ineffective. The destruction of the Rh positive erythrocytes is the initiating agent. The liver cells, partially compressed by dilated sinusoids and by centers of extramedullary hemopoiesis, are called upon to excrete the products of hemolysis. If the excretory function of the hepatic cells is not impaired it is probable that even large amounts of bilirubin can be excreted. In a baby with excessive blood destruction and consequent anoxia this function can readily depreciate. The bile canaliculi become...

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filled with needle-like brownish masses or fine brown granules of bile pigment and biliary stasis ensues. Fatty degeneration is noted and in some areas the liver cells are loaded with fat (figure 1). Other liver functions become depressed. There is hypoproteinemia with attendant loss of circulating fluid. Anoxia becomes more pronounced and the functions of the liver become more deficient. Death ensues in such cases usually in 1-3 days. Prevention of anemia only partially mitigates against this cycle. The most prominent initiating cause is the hemolysis, and this is not prevented by simple repeated transfusions.

The liver changes described above have been repeatedly reported in the earlier literature. Klemperer suggested that therapy be directed at conserving liver function. This was attempted by Hart, who asked a surgeon to perform a substitution on a baby with icterus gravis in 1925 "before the liver cells have been too extensively damaged." The disregard shown in the subsequent literature to Hart's experiment is no more astounding than the fact that Mitchell proved the basic hemolytic origin of erythroblastosis fetalis by demonstrating a specific hemolytic antibody, not associated with normal isoagglutinins, in the serum of mothers of jaundiced babies. This antibody was found in the serum of 51 per cent of the mothers of jaundiced babies and in many of the cord bloods as well, and specifically hemolyzed the cells of the infants in vitro. When the role of
FIG. 1b. Liver—Note the Insipid Bile Collections Within the Liver Cells

FIG. 1c. Liver—Biliary Canaliculus Completely Outlined and Filled with Insipid Bile
isoimmunization in the pathogenesis of erythroblastosis was proven, attention was focussed upon the resulting anemia, and it was not till simple transfusion therapy proved ineffective that the part played by the liver was restressed by Davidsohn. Substitution transfusion was then applied in an attempt to prevent the irreversible liver changes. A search of the literature subsequently disclosed the work of Hart two decades earlier.

The purpose of the substitution procedure is to remove the baby's Rh positive erythrocytes without subjecting it to the perils of shock, and to provide it with circulating and functioning red blood cells which will survive. Three methods to accomplish this aim have thus far been devised.

**FIG. 2. SAGITTAL SINUS TECHNIC**

Rh positive blood withdrawn through anterior fontanelle as Rh negative blood is simultaneously administered through median cephalic vein. Note comparative size of needle in insert.

1. THE SAGITTAL SINUS ROUTE

The substitution transfusion using the sagittal sinus as the route for bleeding (figure 2) is similar to the method employed for Hart.

**Technic**

1. The infant is immobilized.
2. A superficial vein is exposed, a cannula inserted, and an infusion of isotonic sodium chloride or compatible human plasma is given by gravity.
3. A ½ inch, 19 gage needle is inserted into the longitudinal sinus through the anterior fontanelle and withdrawal is performed by syringe.
4. The first and last specimens removed are saved for differential agglutination tests. The other specimens are discarded but a count is kept of the amount of blood withdrawn.
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5. After 50 cc. of blood have been withdrawn, compatible Rh negative blood replaces the infusion.
6. When an estimated substitution of about 85 per cent has been accomplished, the needle is removed from the sinus. The estimate is based upon the infant’s weight, figuring the blood volume as 10 per cent.
   If 1 blood volume has been removed and replaced a substitution of 63 per cent has been achieved. If 1 volumes have been exchanged, a substitution of 86 per cent has been accomplished.
7. The usual procedure is to remove 500 cc. of blood, replacing with 375 cc. of Rh negative blood.
8. During the procedure, 10 cc. of 10 per cent calcium gluconate are injected by syringe through the cannula in the vein. This tends to counteract the effects of the large amount of citrate in the infused blood as well as to replace some of the calcium removed in the bleeding process.

Since this method requires the insertion of a needle into the sagittal sinus, some pediatricians have expressed fear of possible brain injury. It is agreed that care must be employed with this or any therapeutic method, but in our experience the use of a short needle and the limiting of the use of the sinus to blood withdrawal, definitely preclude the chance of subdural hemorrhage or lasting trauma to the adjacent brain tissue.

II. THE RADIAL ARTERY ROUTE

The radial artery (figure 3) was first used for this purpose by Polayes in an attempt to find an alternative method. The heparinization of the infant was subsequently suggested by Vogel who experienced difficulty in bleeding from the artery.

Technic
1. The infusion is set up in the usual way.
2. The infant’s hand is extended at the wrist and the radial artery exposed.
3. The artery is cannulated and the blood permitted to drip into test tubes or other receptacles for testing and discard. A count is maintained of the amount of blood removed.
4. Occasionally the vessel is too small to admit a cannula. It may then be nicked and permitted to bleed directly into the test tubes. If bleeding slows, gentle rubbing of the vessel with a gauze sponge will remove the clot and reinitiate free flow of blood.
5. When the substitution has been accomplished the artery may either be ligated, or bleeding controlled by a pressure bandage.
6. Calcium gluconate is used in the usual way.

Some objections can also be raised to this technic. Anomalies in this region are uncommon, and there is usually a good anastomosis with the interosseous and ulnar arteries to maintain the circulation in the hand. However, if such an anomaly did exist, there could be some impairment of circulation. This can be prevented by the simple precaution of tying the artery before it is cut to see if there is any change in color or temperature of the hand. If there is no apparent change, the artery may be used for bleeding. If there is a change in the hand, one of the other routes for bleeding should be chosen.

Objection has been raised to the use of heparin in this procedure. We have found this drug unnecessary and have experienced no greater difficulty without it than with it. In view of Potter’s findings that silent intracranial injury is common in the newborn it would appear that heparin is not only unnecessary but risky as well. Wiener states that heparinization is necessary to obtain free bleeding and that it is not dangerous since it is washed out of the circulation in the process of substitution.
FIG. 3. RADIAL ARTERY TECHNIC
Cannula in radial artery with bleeding into collecting test-tube.

III. THE UMBILICAL VEIN ROUTE

Recently a third method of substitution has been devised (figure 4). The umbilical vein has long been used for transfusion immediately at birth,25, 26 but Diamond27 has suggested that the vessel may be used for alternate bleeding and
replacement, or for bleeding while the transfusion is given through a superficial vein. We have found this technic effective and no more difficult than the other methods. The use of the umbilical vein has shown that it and the ductus venosus remain open, at least anatomically, for considerably longer than formerly supposed. We have performed the substitution by this technic as late as 36 hours after birth, with no appreciable increase in technical difficulty. With this method, too, heparin has been suggested. Again we have found it unnecessary and believe it to be risky.

Technic

1. The umbilical cord is cut at the tie and the vein located. If there is a thrombus in the vein it is removed.
2. A pliable plastic catheter, with a bore just large enough to permit the passage of a 19 gage needle, is introduced into the vein. Occasionally there is some resistance at the skin level, but with a minimum of manipulation the catheter will pass easily through the umbilical vein and ductus venosus into the inferior vena cava.
3. When the catheter reaches the vena cava a show of blood appears at the outlet.
4. A 19 gage needle is fitted snugly into the outlet of the catheter and attached to two three-way valves in series. To each valve a length of rubber tubing is attached, one leading to the discard bottle, the other to the infusion bottle.
5. Fifty cc. of blood are withdrawn by syringe and then equal amounts alternatingly removed and replaced until the desired substitution has been accomplished.
6. Calcium gluconate is then injected through the catheter, which is then removed, and the cord is retied.

We have experienced no complications with this method. One must remember, however, that infection of the umbilical vein is one of the common causes of sepsis.
in the newborn, and therefore extra precautions are needed. Antibiotic therapy is given routinely after this method is used, and occasional idiosyncrasies may be encountered. The possibility of dislodging a partially adherent thrombus with subsequent embolization must also be kept in mind, although no such event has yet been reported.

In consideration of the respective merits of the 3 routes here described, it is believed that none is completely without risk, yet any one may be used with safety if care is exercised. It is suggested that the pediatrician or hematologist who may be called upon to perform substitutions attempt to familiarize himself with all 3 methods, so that if there is difficulty with one route an alternative technic will be possible.

It appears wise to prohibit breast feeding in all of these cases. It has been shown that the maternal antibody can appear in the milk and it is assumed that if these substances are absorbed unchanged in the newborn digestive tract they may add to the hemolysis.

Occasionally an infant whose blood has been substituted may show a secondary drop in hemoglobin 6-8 weeks later. This is due to the gradual exhaustion of the transfused erythrocytes and the retarded resumption of full blood formation by the bone marrow. A single transfusion, even of Rh positive blood, will prove corrective at this time.

INDICATIONS FOR TREATMENT

We do not believe that substitution should be performed as a routine treatment for erythroblastosis fetalis. Certain criteria have been established which are presumptive of the imminence of severe erythroblastosis either in late pregnancy or in the early neonatal period.

1. Before Birth

A. History of Previous Erythroblastosis. Multiparity is an important predisposing factor. This is the most important single fact in predetermining the fate of the current pregnancy. Potter states that erythroblastosis is ten times more frequent in multiparous than in primiparous women. Unless the father is heterozygous, the illness will reappear with increasing severity in each successive pregnancy.

B. Serologic Studies. The mere demonstration of Rh incompatibility in a family is not sufficient indication of impending disease in the fetus or newborn. It is especially important to demonstrate antibodies in the mother's serum during the pregnancy. These, too, have been found without subsequent illness in the offspring. If the tests are repeated at regular intervals and the concentration of antibody rises steadily it may be assumed that the agglutinin is not residual from a previous immunization but is related to the current pregnancy. This should alert the obstetrician to the possibility of erythroblastosis so that he may be prepared to have a substitution performed if it is proved necessary.

C. Additional Criteria. (1) A history of repeated stillbirths or late miscarriages. (2) Possible previous immunization of the mother by transfusion. (3) Increase in mother's uric acid and icterus index. (4) Excessive enlargement of the uterus. (5) Edema of the fetal scalp as visualized by x-ray.

2. At Birth

A. Physical Examination. Icteric amniotic fluid, large pale placenta, golden yellow vernix caseosa, splenomegaly and jaundice or anemia in a baby whose mother gives a typical history or serologic picture, may be taken as evidence of actual disease and indication for immediate treatment.

B. Laboratory Findings. The demonstration of maternal antibody in the umbilical cord blood and the
sensitization of the cord erythrocytes with blocking antibody are indications of impending and actual hemolysis. These do not, however, indicate the ability of the infant to excrete the products of such hemolysis. This function can better be demonstrated by changes in the icterus index and the number of nucleated red blood cells. In the absence of direct evidence of illness we repeat these tests every 2 hours and treat the infant only if the icterus index rises and the number of nucleated red cells fail to drop, or if clinical evidence of erythroblastosis begins to appear. If these indications do not appear within the first 24 hours substitution will not be needed, and the infant will recover with expectant treatment.

The Rh incompatibility is responsible for erythroblastosis in 92 per cent of the cases. The remaining cases result from immunization against the A or B isoagglutinogens, against the Hr factor or against subgroups of the Rh factor. Treatment is the same except that the blood should be chosen on the basis of compatibility with the mother's serum. Blood of the same group as the infant is preferred, but if not available, group O cells suspended in compatible plasma may be used.

CONCLUSIONS

The basic pathology of erythroblastosis fetalis necessitating treatment by blood substitution is described. The role of the liver in the pathogenesis of the illness is illustrated.

The technics of 3 methods of blood substitution are described and illustrated. The indications for therapy are enumerated.

Twenty-seven infants have been treated by substitution transfusion. Six of these died, but 4 of the 6 were not treated until past the 24 hour period and until jaundice and toxicity were marked. Of the remaining 2, 2 had a tentorial laceration with massive hemorrhage as an obstetric accident. Among the 23 survivors there have been no sequelae. The oldest infant was born in May, 1945.

REFERENCES

HARRY WALLERSTEIN

26 DIAMOND, L. K.: Personal communication.
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