COMMENTARY


Comments by Howard A. Pearson, MD, FAAP

ABSTRACT OF ORIGINAL ARTICLE. The treatment of hemolytic anemia of the newborn often requires support by compatible blood transfusions. Before the discovery of the Rh factor such blood was often only ABO compatible, and for convenience, the patient’s father, who we now know is always Rh positive, was often used as the donor. We noted that the infant’s hemoglobin level often fell rapidly, even with repeated transfusions. Because Rh positive cells are destroyed much more rapidly than Rh negative cells, it seemed logical to use only Rh negative blood as a means to achieve the highest blood levels for protection of the patient, and we began to do this after 1941.

We have recently been able to show that the serum of severely affected infants contains free maternal anti Rh agglutinins and the infant’s red cells are often completely coated with this antibody. The removal of much of the baby’s blood should theoretically diminish the damage resulting from this antibody. Such reasoning lead us to try replacement transfusion as treatment for erythroblastosis. Although it is not a new procedure, to perform it in a newborn adds difficulty to an inherently difficult technic. Earlier methods employed the longitudinal sinus and a peripheral vein or a vein and an artery, requiring prolonged exposure of the infant on an operating table with resultant cold exposure. To prevent clotting, patients also received heparin with its risk of hemorrhage.

The pediatrician cannot help but be attracted to the large and readily accessible vein in the umbilical cord. The development of a bland polyethylene catheter by Dr Ingraham of our neurosurgery department overcame some of the major difficulties of the exsanguination procedure. This catheter can be easily threaded through the umbilical vein into the vena cava through the ductus venosus or by-passing the ductus venosus into the portal vein. The catheter is connected to a needle and then to a three way stopcock. The first valve of the stopcock is connected by a tube to an exhaust pail. The second valve is connected to a bottle of blood and the third to a syringe. By alternate maneuvers of first removing and then putting in blood, 20 cc at a time, the infant can be gradually exsanguinated and most of its blood volume replaced with relatively little trauma. The procedure is carried out with the baby in a warm Hess bed with oxygen administration as needed. We usually use about a pint of Rh negative blood and the procedure takes an hour to an hour and a half. By actual measurement this replaces 90 to 95% of the infant’s own red cells which are coated with antibody. At the end of the procedure, the infant is given calcium to overcome the alkalotic tetany that might result from the sodium citrate in the blood.

In a quarter of cases, it is necessary to transfuse an infant again in the 2nd-4th week because of anemia, but we have rarely had to offer more than a simple transfusion. Infants can be discharged with the mother, sometimes before the eighth day has passed. Previously, the average period of hospitalization for infants with severe erythroblastosis requiring multiple transfusions was three weeks or more, during which time secondary infections could occur.

Not every infant with erythroblastosis requires replacement transfusion and in the past year we have treated only about one in eight babies sent to us. We insist that we receive a specimen of the mother’s blood to prove that the mother has Rh agglutinins which can be on the infant’s Rh positive red cells. Further evaluation is based on clinical signs: anemia, jaundice, edema, and hepatosplenomegaly. The presence of these clinical signs with antibodies in the mother’s circulation implies the need for immediate replacement transfusion.

Even in the absence of these clinical signs, certain laboratory evidence may indicate the need for immediate treatment. If the baby’s Rh positive cells are coated with antibody and the baby has free antibody in its circulation, our selected data over several years indicate that replacement transfusion should be done because such infants quite regularly develop severe symptoms within the second to fourth day of life. The absence of clinical signs and the absence of the laboratory findings suggest that the infant will do well enough without such drastic treatment.

As a background for an evaluation of our present mode of therapy, we have statistics collected over the past 15 years. Before 1941, taking all of the infants sent to us, there was a 35–40% mortality. Between 1941 and 1946, with Rh negative transfusions, our mortality dropped to 30% or less. Our present data covers about 15 months of experience and 85 infants treated personally by replacement transfusions through the umbilical vein. Sixty-five are now living and well with follow ups of 3 to 15 months. A number of the surviving infants came from families where a previous infant had died of erythroblastosis. In such families the chance of a subsequent affected infant surviving is less than 10%. The survival of such children in our series was 70%. Seven patients died, but not of erythroblastosis. The causes were immaturity, tentorial tears or other factors which cannot be directly related to erythroblastosis. Seven patients died of the disease; six of these showed kernicterus.

From the Yale University School of Medicine, Department of Pediatrics, New Haven, Connecticut.
Received for publication Mar 19, 1998; accepted Mar 19, 1998.
Address correspondence to: Howard A. Pearson, MD, FAAP, Yale University School of Medicine, Department of Pediatrics, 333 Cedar St, New Haven, CT 06520.
This mode of therapy has the advantage of ease and greater safety in performance. An added advantage is earlier discharge from the hospital at 7 or 8 days rather than 2 to 3 weeks. Although this is not a panacea for erythroblastosis, replacement transfusion seems to be a better method of treatment for many cases.

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This seminal article was delivered by Dr Diamond on the occasion of his receiving the Mead Johnson award in 1946. The article is absolutely characteristic of Diamond, who through out his long career, was a quintessential clinician and clinical investigator. Diamond’s interest in pediatric hematology began early in his career, an interest fostered by his chief and mentor at the Boston Children’s Hospital, Dr Kenneth Blackfan. In 1932, while still in training at Children’s, Diamond, with Baty and Blackfan, wrote a landmark 60-page paper presenting the hypothesis that four different syndromes—stillbirth with erythroblastosis in the tissues, fetal hydrops, congenital anemia of the newborn, and icterus gravis—were different manifestations of a single pathophysiologic process that they designated erythroblastosis fetalis. This earlier paper was published in the Journal of Pediatrics, which, as noted elsewhere in this semicentenary volume, was then the official organ of the American Academy of Pediatrics.

Eight years later, Landsteiner and Weiner discovered the Rh factor. Shortly after this, Levine and associates showed that erythroblastosis fetalis was caused by immunization of an Rh-negative mother by an Rh-positive fetus. Diamond and associates rapidly developed techniques to identify and quantitate Rh antibody in the serum of mothers and their affected infants to provide laboratory backup for clinical interventions. He believed that these antibodies in the infant caused severe anemia, which was only poorly controlled by transfusions of Rh-positive blood. In the early 1940s, he began to use only Rh-negative blood to transfuse erythroblastotic infants, but was able to reduce the high mortality of the condition only modestly.

Diamond then reasoned that if the affected infant’s blood could be totally replaced, much of the offending antibody would be removed. Replacement transfusions had been performed previously, usually by removing blood from the sagittal sinus while infusing replacement blood into a peripheral vein. This was a hazardous, difficult procedure. Seeking an alternative, Diamond was “attracted to the large and accessible vein in the umbilical cord.” The availability of plastic catheters that were being tested by his colleagues in neurosurgery at Children’s Hospital made it possible to easily cannulate the umbilical vein to accomplish safe and effective isovolemic exchange transfusions. In only 15 months, he was able to report in this paper a dramatically reduced mortality rate in severely affected infants treated with replacement transfusions.

The procedure was relatively easy, and within a short period, it was being performed by pediatricians throughout the world. However, as pointed out by Diamond, even with early replacement transfusions, ~10% of these children still died because of kernicterus. In 1949, Dr Patrick Mollison suggested to Dr Diamond that multiple exchange transfusions might be used to prevent extreme hyperbilirubinemia, thus preventing kernicterus. At this time, >10% of severe mental retardation could be attributed to kernicterus. Considering that most infants who developed clinical kernicterus died, this was an enormous pediatric problem. Diamond and associates then developed criteria for exchange transfusions that addressed both the problem of anemia and the prevention of hyperbilirubinemia. Exchange transfusion, using Diamond’s umbilical vein technique, became a standard part of the armamentarium of the general pediatrician in hospitals around the country, and tens of thousands of babies were saved.

A final problem remained: that of intrauterine death of severely affected infants. Diamond and associates developed criteria for early delivery to prevent late fetal deaths that were of some benefit. However, it was the work of Liley who showed the prognostic value of amniotic fluid spectrometry to identify infants at high risk of intrauterine death that set the stage for his development of intrauterine transfusions that effectively prevented otherwise inevitable intrauterine deaths.

The final chapter of this story was the demonstration by Freda that postpartum treatment of Rh-negative women with anti-Rh immunoglobulin, could prevent initial sensitization and virtually all cases of Rh erythroblastosis fetalis. In 1968, in a commentary in Pediatrics, Dr Diamond wrote, “Rarely has it been our good fortune to have a disease recognized, its cause clearly determined, its treatment successfully developed to an extent and then its prevention found, all in one generation.” Typically, he did not mention his essential role in this great medical triumph.

It is, perhaps, not inappropriate to mention something of the circumstances under which Dr Diamond worked under during the time of some of his greatest accomplishments. In the late 1930s and early 1940s, although full-time at Children’s Hospital, he had to supplement a “meager” academic salary by pediatric practice. His personal involvement and commitment to his clinical research is apparent from remarks in the 1946 paper: “We have statistics collected over the past 15 years or more. All cases have been observed personally, [and] our present data covers [sic] about 15 months of experience and 95 infants treated personally by replacement transfusions.”

Dr Kenneth Blackfan’s untimely death from lung cancer occurred in 1941. At the same time, the World War II mobilization of physicians more than decimated the clinical staff at Children’s Hospital. It fell to a small group of pediatricians, including Diamond, to carry the load. During the war, he was also called on to serve for three hectic years as the first technical director of the National Blood Program of the American Red Cross. Diamond’s accomplishments were recognized by honors from around the world. It seems remarkable
that he did not attain a full professorship at Harvard until he became emeritus in 1968.

REFERENCES

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Comments by Joseph F. Fitzgerald, MD

ABSTRACT OF ORIGINAL ARTICLE. The clinical syndrome known as Hirschsprung disease (HD), or congenital megacolon, had been recognized for more than a century. The pathogenesis of the dilatation/hypertrophy of the colon without mechanical obstruction was puzzling, and the subject of great debate. Virtually all infants and children affected with this disorder died.

The authors studied 26 patients with congenital megacolon admitted to Boston Children’s Hospital during a 5-year period, from 1943 through 1947. Careful contrast radiographic study of the distal colon in all 26 revealed a functional obstruction produced by a dyskinesia of the rectum. This was detected by running a small amount of barium slowly into the rectum with the patient in an oblique position. A portion of the rectum/rectosigmoid was consistently subnormal in caliber. Barium then was allowed to run through this narrowed area into the dilated colon. The authors interpreted the radiographic findings as evidence of a physiologic partial obstruction of the rectum/rectosigmoid.

Colostomies were performed in the dilated portion of the colon in 3 early patients, and all symptoms/signs of HD disappeared in each instance. These returned, however, with closure of the colostomies and persisted until the ostomy was reestablished. Colostomies then were performed in an additional 12 patients, and each was relieved of symptoms with restoration of a normal-caliber colon. The authors recognized that the distal obstructing segment would have to be removed before the colostomy could be closed.

They devised a special “pull-through” form of resection and tested it in the laboratory. The operation was performed subsequently on 23 patients, with no fatalities. Closure of the colostomy was possible in all but 2. The authors outlined the operation in detail in the article. Three infants, the youngest being 2 months old, tolerated a one-stage operation. The authors indicated that all patients subsequently demonstrated the urge to defecate and had normal bowel control.

Patients with HD have a physiologic obstruction in the nondilated segment of colon. Early colostomy relieves the symptoms/signs of obstruction, and removal of the narrowed segment results in cure.

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This watershed article described in fine detail the evaluation and management of patients with congenital megacolon. The authors included additional early observations in their article. They observed that the onset of symptoms was in the first week of life in all patients where early history was known (25/26). This was similar to the 2 patients described by Harald Hirschsprung in 1888.1 This supported a congenital origin. They noted that there was a marked male predominance (22/26; 84%). Despite the fact that impacted stool was present in the colon on abdominal examination, digital examination of the rectum revealed an empty vault in 24 of 26 patients (96%). This also was an observation shared by Hirschsprung. The absence of ganglion cells was not mentioned in the article, even though this fact was known at the time.

Frederick Ruysch is actually credited with describing the first case of HD in the medical literature in 1691.2 He described a 5-year-old girl with an “enormous dilatation of the colon” at autopsy. Hirschsprung delivered his classic paper 2 centuries later. Hirschsprung, as stated above, did note a distal site of constriction in an 11-month-old child who came to autopsy. Despite this, his attention was directed to...
Howard A. Pearson
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