ERYTHROBLASTOSIS FETALIS

C. Edwin Kinley, '56

Definition.

Erythroblastosis Fetalis is a hemolytic disease of fetal or neonatal life due to fetal-maternal blood group incompatibility; the fetus having a blood factor that its mother lacks, and the mother producing antibodies against that factor. These maternal antibodies are capable of agglutinating the RBC's of both the fetus and the father. Erythroblastosis Fetalis includes at least three clinical types: (a) hydrops fetalis, (b) icterus gravis of the newborn, and (c) hemolytic anemia of the newborn.

Incidence.

Erythroblastosis Fetalis occurs about once in every 250 deliveries, and is responsible for about 3% of infant deaths. (1)

Etiology.

Classically, the development of Erythroblastosis Fetalis is based upon the following sequence of events: (a) immunization of an Rh negative mother by the Rh positive RBC's of the fetus, or on occassion by the transfusion of an Rh negative woman with Rh positive blood. (b) Production by the mother of an anti-Rh agglutinin. (c) Passage of this agglutinin across the placental barrier into the fetal circulation. (d) Destruction of fetal RBC's due to a specific reaction between the fetal Rh antigen and the maternal Rh agglutinin. (2)

It is now recognized that Erythroblastosis Fetalis is caused by incompatibility of several other of the 9 blood grouping systems, most common of which appears to be incompatibility in the ABO system. In fact ABO incompatibility may be a more common cause of Erythroblastosis Fetalis than incompatibility in the Rh system, but it usually escapes notice because it is rarely accompanied by significant anemia and extremely rarely by hydrops fetalis.

Pathophysiology.

There is reason to believe that transfer of small numbers of fetal RBC's across the placenta into the maternal circulation occurs in most pregnancies. When the fetal cells contain an antigenic factor not possessed by the maternal cells, transplacental passage of fetal RBC's results in the appearance in the mother's plasma of antibodies to the fetal antigenic factor. These maternal antibodies may in turn pass through the placenta into the fetal circulation and there cause rapid destruction of fetal RBC's. That the rapid blood destruction does not usually kill the baby in utero is due to two important circumstances: (a) the fetus is usually able by expansion of blood forming tissue i.e. extramedullary erythropoiesis in the spleen and liver, to manufacture RBC's fast enough to establish an equilibrium between blood destruc-

tion and blood formation. Even so, there may be a severe degree of anemia at birth; (b) the placenta usually removes quite effectively the toxic by-products of red cell destruction.

Birth, which cuts off the introduction of further maternal antibody, brings about two problems: (a) A progressive anemia, consequent upon a rapid decrease in RBC production; this anemia is seldom difficult to recognize or to deal with; (b) Much more important is the inability of most newborn babies to excrete bilirubin, due to hepatic immaturity at birth. Bilirubin accumulates rapidly in the blood and commonly reaches within 48 hours higher levels than are seen in any other clinical condition, even complete obliteration of the bile ducts; serum bilirubin levels between 40-80 mg% being not uncommon. Bilirubin, or something closely related to it, is very damaging to the baby and as he is unable to excrete it in the first 48 hours (or longer if he is premature) it's production must be reduced if brain damage is to be avoided. Exchange transfusion, by removing most of the fetal RBC's and replacing them with RBC's compatible with the maternal antibody, greatly reduces bilirubin formation. Even so, the bilirubin may again rise to dangerous levels, necessitating a second exchange transfusion, not only for removing fetal RBC's that may have been formed subsequent to the first exchange transfusion, but also for removing about one-third of the total bilirubin.

PATHOLOGY.

(a) **Hydrops Fetalis.** The infant is almost always born dead. There is usually no jaundice, unless the infant lived a few hours after birth. There is generalized edema as a result of endothelial anoxia and a hypoproteinemia of hepatic origin; this endothelial anoxia may also result in purpuric manifestations. The blood shows anemia, with an excess of immature erythrocytes in the circulation. The bone marrow shows erythroblastic hyperplasia, and there is evidence of extramedullary erythropoiesis especially in liver and spleen. There may be hyperplasia of the Islets of Langerhans, lipoid infiltration of the adrenal cortex, and atrophy of lymphatic tissue.

(b). **Infants who die of Erythroblastosis Fetalis after the first day of life.** In these cases the characteristic findings are jaundice and kernicterus (i.e., jaundice of the cerebrospinal nuclei). There may be widespread hemosiderosis of all tissues. The most common gross findings are enlargement of the spleen and usually also of the liver.

(c) **The Placentas** of erythroblastotic infants are usually enlarged and edematous, especially in fetal hydrops; the normal fetal-placental weight ratio of 6:I may be decreased to as little as 3:1. The villi show hydropic degeneration. The placentas of infants suffering from the milder forms of Erythroblastosis Fetalis may show little change from the normal.

(d) A few words on the etiology of kernicterus. There are many theories on the etiology of kernicterus. All theories are alike in suggesting that the nervous tissue is first injured in some way and then stained. Kernicterus is associated with both the physiological jaundice of the newborn and with the jaundice of Erythroblastosis. About 50% of all infants develop physiological jaundice. Thus in about one half of all cases of Erythroblastosis Fetalis there exists the possibility of a co-existing physiological jaundice. If one remembers that physiological jaundice may be severe, it becomes evident that an Rh positive infant of a sensitized Rh negative mother may at times develop an intense jaundice and even kernicterus, without actually having Erythroblastosis.

Physiological jaundice has been attributed to hepatic immaturity at birth. The maturity of the liver at birth determines to a large extent the presence or absence of neonatal jaundice in the premature infant, the full-term infant, and the infant with Erythroblastosis Fetalis. Thus in E.F. all degrees of correlation may exist between the Comb's Test, hemolytic anemia and the degree of jaundice. The more immature the liver the more intense the jaundice and the more severe it's complications.

In any theory of the etiology of kernicterus the following facts must be taken into account (4):

(a) Kernicterus does not develop before birth. The placenta is apparently able to maintain the fetal bilirubin serum level below 10 mg%, and the development of kernicterus is unlikely with a serum bilirubin level less than 20 mg%; (b) Kernicterus has never been observed to develop after the first few neonatal days; (c) Premature and even some term infants may develop kernicterus. It has been said that physiological jaundice of the newborn is responsible for more cases of kernicterus than E.F.; (d) Exchange transfusion has effectively reduced the incidence of kernicterus in cases of E.F. In this respect it must be pointed out that in the infant with E.F. there exists a high correlation between the intensity of the bilirubinemia and the development of kernicterus.

The most acceptable theory at present regarding the etiology of kernicterus states (a) During the first few days of life there is an increased vascular permeability in hemolytic babies, and in non-hemolytic premature babies; (b) Hyperbilirubinemia during this time may result in the deposition of bile in nervous and other tissues, by a process of mass action. (6)

Clinical Manifestations.

(a) **In the mother.** There may be a history of previous erythroblastotic babies. Or we may find evidence of anit-Rh agglutinins in the Rh negative wife of an Rh positive father. Toxemia of pregnancy is not common in the mothers of erythroblastotic babies; when it does occur it is usually mild, and is usually associated with fetal hydrops. Other complications are extremely common with hydrops fetalis, and include dystocia, hydram-

nios and premature labour. The large placenta may cause difficulty in the third stage.

(b) **In the fetus.** Intrauterine diagnosis of fetal hydrops can be made by the X-ray appearance of a halo around the infant's scalp, and the characteristic Budda attitude. At birth the diagnosis of fetal hydrops is easy, but congenital syphillis and congenital abnormalities of the heart and kidneys must be ruled out. In icterus gravis the baby is born jaundiced, and the vernix caseosa and amiotic fluid may be stained a deep yellow. Purpura may be noted. The liver is always palpable, and usually the spleen. In most cases of E.F. jaundice is not present at birth, but becomes noticeable in the first day or two. In this regard it should be noted that jaundice developing in the first 24 hours of life nearly always means E.F., irrespective of whether the mother is Rh positive or negative. As the jaundice deepens signs of nervous system involvment may appear, in the form of lethargy, poor feeding, and loss of the Moro reflex. In severe cases there may be extreme hypotonia, spasms or convulsions.

Diagnosis.

The diagnosis of E.F. depends on what fetal blood factor is the cause in the particular case (II). In perhaps 80% of cases it is the Rh factor. In such a case the mother is Rh negative and routine prenatal testing for agglutinins in her blood will reveal that she is one of the 5% of Rh negative women who become sensitized to the Rh factor during pregnancy. The physician then obtains a sample of cord blood at birth, on which the Combs' Test is done. A positive Combs' Test in the newborn always means E.F. Thus the diagnosis is no problem when the desease is due to Rh incompatibility. In about 20% of cases of E.F. the cause is not Rh incompatibility, and the mother is usually Rh positive; the physician is not forewarned by the routine pregnancy serologic tests, and the infant nearly always looks perfectly normal at birth. However, the baby becomes jaundiced during the first 24 hours of life. Blood is drawn from mother and baby; both bloods are typed, and a Combs' Test is done on the infant's blood. If the mother's blood is Rh positive and the Combs' Test is also positive, the diagnosis is made of E.F. due to incompatibility in one of the uncommon blood grouping systems, such as Kell, Lewis or MNS. If, however, the mother's blood is Rh positive but the Combs' Test is negative, and the fetal blood incompatible with the mother's blood in the ABO system, it is almost certain that the case is one of that fairly large group caused by a major blood group incompatibility. ABO E.F. is not generally predictable before birth, and it is not known why the Combs' Test is negative. Absolute diagnosis is difficult, but two findings present: (a) serum bilirubin rising to at least 15 mg% in the first 24 hours, and (b) an incompatible antibody in the baby's serum (i.e. anti-A or anti-B). Another finding that is of some help is the almost invariable presence in the mother's serum of a very high titre of hyperimmune anti-A or anti-B.

The following observation was made regarding the relative frequency of E.F. due to ABO incompatibility: In the Beth Israel Hospital over a six months period, all nurses working in the nurseries were instructed to look especially for and report all infants who became jaundiced during the first 36 hours of life. Of 1550 infants delivered during this period, 19 were subsequently reported as jaundiced; 7 cases were E.F. due to Rh incompatibility, and 11 were diagnosed as E.F. due to ABO incompatibility; in one case no blood group incompatibility was demonstrated. At another hospital in the district, with about equal numbers of deliveries but where daily reports of jaundice were not required from the nurses, only 2 cases of E.F. due to ABO incompatibility were noted during the same period. These authors conclude that E.F. due to ABO incompatibility is probably much more common than is generally believed, but is not diagnosed as such either because the icterus in the new-born infant is attributed to a physiological jaundice, or is not considered significant once the possibility of Rh incompatibility has been ruled out. (16)

Course of the Desease

Maternal isoimmunization may result in intrauterine death of the fetus (i.e. fetal hydrops), which is commonly referred to as the severe form of the disease; or the case may be one of icterus gravis, with or without kernicterus, or of hemolytic anemia of the newborn, cases which have been called mild forms of the disease. It is frequently assumed that in any one family successive Rh positive infants tend to be progressively more severely affected by the hemolytic process. This is now known to be not entirely true.

The following points should be noted (12): (a) One group of mothers tends to have infants with with mild forms of the disease, and even their second and third children are predominantely mildly affected. A second, smaller group tends to have severely affected infants in all cases. One large study indicated that if the first affected child is a mild case, then in 80% of cases the next child will also be mildly affected. But if the first child be severely affected, then in 80% of cases the next child will also be severely affected. (b) Mothers tending to have severely affected infants have fewer children than do mothers tending to have mildly affected infants, before the appearance of their first erythroblastotic baby; this may indicate that they are more readily sensitized. (c) There are some intermediate families in which the disease tends in successive infants to be more severe. (d) Rh negative women who have had transfusions with Rh positive blood tend to have severely infected infants; (e) E.F. due to ABO incompatibility occurs in first born infants with about the same frequency as in later infants (4), (15).

Treatment of Erythroblastosis Fetalis.

(a) **Treatment during pregnancy.**

In spite of a great deal of investigative effort there is still no agent of real value in the prenatal treatment of E.F. Diethylenesulfonate, ex-

change transfusion of the mother, the use of desentizing injections, and the use of ACTH and Cortisone have all proved to be useless (13). Some studies seem to show an increased number of normal babies following the injection into the sensitized mother of so-called Rh hapten(5); but the method requires further investigation (3).

Premature delivery in cases of E.F. as a routine procedure is to be condemned (10), for the following reasons: (a) the premature infant has a greater chance of developing kernicterus than the term baby; (b) an occassional baby may die of causes related to prematurity. (c) Cesarean Section may have to be resorted to where rupture of the membranes fails to induce labor. However, individual cases arise in which premature induction of labor should be considered (14). Such a case would be a patient with a history of two or more stillbirths, and whose husband is homozygous Rh positive. A premature delivery should be carried out only in a hospital equipped both for exchange transfusion and for the care of premature babies.

(b) **Treatment during the delivery.** When E.F. is suspected, anageslia and general anaesthesia should not be used during delivery because intrauterine or neonatal asphyxia is present in many of the infants. Local or saddle block anaesthesia should be used. Several inches of umbilical cord should be left for use during exchange transfusion, and the cord be tied as soon after delivery as possible, to prevent transfusion of the infant with the sensitized cells of the placental blood.

(c) **Postnatal treatment.** In the light of present knowledge, the same criteria for treatment should be applied to all cases of E.F., whether due to Rh incompatibility, ABO incompatibility or incompatibility among any other blood grouping system.

The present concensus of opinion holds that exchange transfusion is far superior to simple transfusion. Not only are there more survivors among infants treated with exchange transfusions, but the incidence of kernicterus is lower (10). In one series of 62 infants treated with exchange transfusion, only 4 developed kernicterus, 3 of them being premature.

Technique of Exchange Transfusion. Details will not be presented. Theoretically, replacement of the infant's RBC's should be complete; but since withdrawal and administration of blood must be carried out simultaneously, this can never be achieved in practice. For convenience 500c.c. of blood are used, which amount is about twice the infant's blood volume, and is sufficient for about 85% replacement. The umbilical vein may be catheterized with a 20 gauge polyethylene tubing, and through this blood is alternately withdrawn and injected in 20 c.c. amounts. Other sites for transfusion may be utilized. The blood is first withdrawn because of the danger of overloading the infant's circulation, and so precipitating a congestive heart failure, and because infant's withstand anoxia quite well. The principle factor in

the reduction of mortality, aside from exchange transfusion itself, has been the realization that many of the sickest infants are actually on the verge of a congestive heart failure, and that failure may be precipitated by putting in more blood than is withdrawn (7). By using concentrated blood, i.e. blood from which some of the citrated plasma has been removed, relatively high Hb levels can be attained even though the same amount of blood is injected as is withdrawn.

During the exchange transfusion, calcium gluconate is administered i-v in quantities of 1 c.c. of a 10% soln for each 100 c.c. of blood given (9). This is done because of the danger of hypocalcemia resulting from the calcium of the injected blood being held in a non-ionizable form by citrate, and by excess citrate in the injected blood binding the free calcium of the infant's serum.

Hyperpotassemia may also result from exchange transfusion (8). In stored blood, potassium gradually leaves the cells and passes into the plasma, where the potassium level may rise from 5 mEq/L to 10 mEq/L in a two week period. It is generally agreed that serum K levels of greater than 7 mEq/L may be toxic to the heart, especially in the presence of hypo-calcemia which may augment the EKG changes of hyperpotassemia. The potential danger of hyperpotassemia should be minimized by the use of blood not more than 7 days old, and by the adequate concurrent administration of calcium gluconate. It has been recommended that serial EKG's be taken during exchange transfusion, so that immediate records of Ca or K electrolyte disturbances may be had.

Indications for exchange transfusion. (a) Any clinical evidence of E.F. is an indication for immediate exchange transfusion e.g. jaundice developing in the first 24 hours of life, hepatosplenomegaly, edema; (b) an erythroblastotic baby weighing less than 5½ lbs. at birth; (c) an erythroblastotic baby with a cord Hb below 15 gm%; (d) any baby born to a woman who has previously had a severely affected erythroblastotic infant; (e) a maternal anti-Rh titre of 1:64 or greater; (f) if the serum bilirubin reaches 10 mg% in the first 12 hours; after this time the aim should be to keep the serum bilirubin below 20 mg%. For this a second or even a third or fourth transfusion may be necessary.

In Summary. If sensitization to the Rh factor is demonstrated in a pregnant woman, E.F. should be anticipated in the baby and complete preparation should be made for it's arrival. Advance preparation means preparation for exchange transfusion; nothing else can be done before the birth of the infant. Careful inspection of all infants in the first day or two of life will reveal certain mild cases of E.F., especially those due to ABO incompatibility. The overall mortality in infants treated with exchange transfusion is about 13%, as compared with a mortality of 80 - 90% in infants treated without exchange transfusion.

References:

1　DeLee: Textbook of Obstetrics 10th Edition.
2　Nelson: Textbook of Pediatrics, 6th Edition.
3　Review of Current Literature: J. of Obs. and Gyn. of Brit. Emp., Dec. 1953.
4.　Black-Staffer, Kambe,Furata and Moloney: Am. J. of Des. of Childh., June 1954.
5.　Carter: Lancet, June 19, 1954.
6.　McGreal: Lancet, June 26, 1954.
7.　Allen and Diamond: J.A.M.A., July 31, 1954.
8.　Miller, McCoord and Clausen: Ped., May, 1954.
9.　Wiener et al.: J. of Ped., Nov. 1954.
10.　Armitage and Mollison: J. of Obs. and Gyn. of Brit Emp., Oct. 1953.
11.　Allen: New Eng. J. of Med., Sept. 11, 1952.
12.　Davies, Gerrard and Waterhouse: Arch. of Des. in Childh., Dec. 1953.
13.　Shanaphy: Am. J. of Obs. and Gyn., Dec. 1952.
14.　Watson, Crosse and Hatchuel: B.M.J., March 20, 1954.
15.　Shamir and Gurevitch: Arch. of Des. in Childh., Aug. 1953.
16.　Yi Yung, Hsia and Gellis: Pediatrics, June 1954.