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THE Rh FACTOR IN HEMOLYTIC DISEASE OF THE NEWBORN

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THIS article is not intended as a comprehensive nor a critical review of the relationship of the Rh factor to hemolytic disease of the newborn, but rather as an introduction to the paper on the "Morality of the Rh factor" to be given by Father Schwitalla. In this paper I will discuss the development of the work which has been done on the Rh factor of the blood in humans, discuss briefly its relationship in hemolytic disease of the newborn and indicate the value of Rh studies particularly in relationship to pregnancy.

In their experiments during and just prior to 1937, Landsteiner and Wiener produced an antibody in rabbits by the injection of monkey blood as an antigen. This new antibody not only agglutinated the red blood cells of monkeys but in addition agglutinated those of certain white humans. This indicated a new factor present in the red cells of certain humans and because it had been developed by the use of the blood of the macacus rhesus monkey the name Rh was given it to indicate the original source of the antigen. Further studies indicated that approximately 85% of white humans possessed this Rh agglutinogen in their red cells and in the other 15% it was absent. They were accordingly designated as Rh positive (containing the Rh agglutinogen) and Rh negative (an absence of the Rh agglutinogen). This newly described factor was not initially considered to be of great importance until in 1939 Wiener and Peters found the antibody to this newly discovered Rh factor in three patients who had severe hemolytic reactions following transfusions of otherwise compatible blood. These patients apparently had been immunized or better, iso-immunized, to the rhesus or Rh factor. Levine and his coworkers then noted the very frequent occurrence of

transfusion reactions in women who had stillbirths or infants with erythro-blastosis fetalis. At this time Levine postulated the very interesting theory that an Rh negative mother who bears an Rh positive fetus became sensitized in some manner to the Rh factor of the fetus and subsequently developed antibodies in her blood to the Rh factor. These antibodies in turn passed through the placenta and into the fetal blood circulation with resulting agglutination and hemolysis of the fetal blood. The intra-uterine hemolysis in the infant then would account for the severe symptoms which were found to be present in erythroblastosis fetalis. Because erythroblastosis fetalis in its varied forms was demon-strated to be the result of fetal and neo-natal hemolysis it is referred to today as hemolytic disease of infants and newborns.

The antibody produced by the artificial immunization of rabbits to monkey blood has certain characteristics which are identical with that of the antibody produced in women delivering infants with hemolytic disease. The antibody produced in humans has been designated anti Rh_o and the erythrocytes which are agglutinated by this antibody are designated as the Rh_o type. Later it was found that there were two and perhaps more factors present in human iso-immunization which were not present in the original immunization of rabbits with monkey blood.

The two additional antibodies which have been detected in humans are given the designations anti Rh^1 and anti Rh^{11} and accordingly, these sera detect the presence or absence of the corresponding three Rh factors in human blood, namely, Rh_o Rh^1 and Rh^{11}. By the use of these three agglutinating sera we can thus differentiate eight Rh types in the first four of which the Rh_o factor is absent and in the last four is present, as follows:

Clinically Rh negative

Rh negative, Rh^1, Rh^{11}, Rh^1 Rh^{11}

Clinically Rh positive

Rh_o, Rh, (Rh_o^{11}), Rh_2 (Rh_o^{11}), Rh_1 Rh_2

in this scheme the Rh_1 and Rh_2 factors are considered to be combi-nations of the Rh_o and Rh^{11} and Rh_o respectively as Rh_o^1 and Rh_o^{11}.

Since the Rh_o factor which corresponds to the original anti-rhesus serum is by far the most antigenic and therefore the most important clinically, it is the presence or absence of this factor which is deter-mined by most of the antiserum on the commercial market. For clinical purposes we may consider any blood in which the Rh_o factor is present to be Rh positive and those in which the Rh_o factor is absent to be Rh negative. This is true in approximately 85% of individuals while the rarer Rh Factors account for only approxi-mately 2% of the white population.

The presence or the absence of the Rh factor in the erythrocytes is hereditarily determined and the Rh factor is transmitted to

offspring as a Mendelian dominant by a pair of allelic genes, Rh (dominant) and rh (recessive). Since every individual possesses a pair of genes from every allelic series of genes one from the father and one from the mother, there are thus three genotypes possible.

Rh Factor Transmission

Types	Genotypes	
Rh—	rh rh	Homozygous
Rh+	Rh Rh	Homozygous
Rh+	Rh rh	Heterozygous

From this we can see that for the entire group of eight Rh types, there are twenty-one possible genatypes. Since the type of blood is determined by the character of the blood of the parent and a gene inherited from each of the father and the mother, the Rh factor is inherited as in the following chart.

Inheritance of the Rh Factor

PARENT		PARENT		CHILD	
Type	Genotype	Type	Genotype	Type	Genotype
Rh—	rh rh	Rh—	rh rh	Rh— (100%)	rh rh
Rh+	Rh Rh	Rh—	rh rh	Rh+ (100%)	Rh rh
Rh+	Rh rh	Rh—	rh rh	Rh+ (50%)	Rh rh
Rh+	Rh Rh	Rh+	Rh Rh	Rh+ (100%)	Rh Rh
Rh+	Rh rh	Rh+	Rh rh	Rh+ (25%)	Rh Rh
				Rh+ (50%)	Rh rh
				Rh— (25%)	rh rh

Levine has described another factor which because of its reciprocal relationship to the Rh factor has been described as the Hr factor. Because of its peculiar reciprocal relationship to the Rh factor, the Hr factor by its presence or absence in the erythrocytes has been used to distinguish homozygous and heterozygous Rh positive blood. In this test erythrocytes from homozygous individuals are not agglutinated by the anti Hr serum.

Recently it has been found that the Rh factor as an antigen may produce more than one type of antibody. This second type of antibody produced is sometimes designated as a blocking antibody which specifically unites with and coats the surface of the Rh positive erythrocytes without inducing physical effective agglutination. In other words the antibody is incomplete because only the first stage of the reaction occurs. The specifically coated Rh positive erythrocytes are now incapable of reacting with the usual anti Rh agglutin and as a result special tests have been described by means of which it is possible to detect the anti Rh agglutin in the usual manner and the so-called blocking antibody as well. The blocking antibody according to Wiener, is of more importance in the production of hemolytic disease than the Rh antibody. The blocking

antibody has a smaller molecule and theoretically passes the placental barrier more readily, and it is strongly antigenic.

Many examples of iso-immunization by repeated transfusions of Rh positive blood into Rh negative recipients are recorded in the literature. Levine has found a definite history of prior transfusions in sixteen of a series of twenty-five cases of hemolytic disease of the newborn in the first born of Rh negative women. Levine has further emphasized the importance of small immunizing doses of blood and has calculated that only .13.cc. of fetal blood is required to immunize the Rh negative mother. As a result of these and other observations we must assume that once an individual is immunized to the Rh factor, either by repeated transfusions, intramuscular injection of blood or by pregnancy, he must be considered as immunized for the remainder of his natural life, and further that with each succeeding exposure to Rh positive blood he will probably produce increasingly greater quantities of antibody. Accordingly, it is important in pediatric practice to administer only Rh negative blood to Rh negative female infants and to minimize the intramuscular injection of blood from any donor who is Rh positive. One or more transfusions of Rh positive blood administered to an Rh negative female infant may prevent her many years later from having one or more normal Rh positive infants. Further, Rh testing is particularly indicated if repeated transfusions are anticipated especially in young females before and during the childbearing period, and in some, past the menopause, if they have borne children, particularly if there is any evidence in the history which would indicate previous immunization to the Rh factor. Humans, as well as experimental animals, differ considerably in the ease with which they become sensitized to various antigens. In humans this is indicated by the fact that approximately one out of ten marriages are of the serologic sequence (Rh positive male, Rh negative female) which is capable of producing infants with hemolytic disease. Actually only one in approximately two-hundred fifty newborns is so affected. Further, sensitization in pregnancy probably increases only with repeated exposures to the Rh factor as an antigen and as a consequence hemolytic disease in the first borne is relatively uncommon unless there is a history of previous exposure to the Rh factor. As a rule we can anticipate one, two, or perhaps more perfectly normal children who may be Rh positive even though the subsequent children are so affected. Hemolytic disease of the newborn is gradually increasing in importance because of two essential factors: first, the diagnosis is made more readily than formerly because of increased diagnostic acumen and additional criteria upon which a diagnosis can be based; and secondly, the lowering mortality in hemolytic disease because of improved methods in treatment such as prompt transfusion. The diagnosis of hemolytic disease of the newborn usually does not present much difficulty. However, there are a number of diseases which must be kept in mind and in the differential diagnosis we must consider congenital syphilis, intra-uterine or post-partum infections of the infant,

certain hemorrhagic disease of the newborn, very rarely congenital mal-
formation of the bile ducts and physiologic icterus which very frequently
occurs in newborn babies.

If we recall that there are various clinical types of hemolytic
disease of the newborn, we are in a much better position to make the
proper clinical diagnosis. These forms of hemolytic disease include
fetal hydrops which is the most severe and has a mortality rate of
approximately 100%, the jaundiced form, and the jaundiced form
anemia and finally, the form which is manifest simply as a hemor-
rhagic diathesis. These various forms are apparently related
genetically and etiologically.

The evidences of hemolytic disease in the infant may be found in the
mother or in the infant. In the parents we would expect the serologic
sequence of an Rh positive father and an Rh negative mother. If the
mother becomes immunized to the blood of the fetus, there will be Rh
antibodies in her blood serum. In some there may possibly be a history
of previous transfusions especially with Rh positive blood or the intra-
muscular injection of blood during infancy. During pregnancy there may
be evidences of hydramnios, death of the fetus and at birth there is fre-
quently yellow amniotic fluid and enlargement of the placenta. The
presence of Rh antibodies in the mother's blood can be possibly used in
a limited way to predict the occurrence of hemolytic disease in the
infant. If no antibody is found or if small amounts are found regularly
the infants will usually have no evidence of hemolytic disease. If large
amounts of antibody or small amounts of antibody are repeatedly found,
the infants may develop some form of hemolytic disease.

Early appearance of large amounts of antibody generally indicates
a serious prognosis for the infant. If these observations are repeatedly
confirmed, it will allow us to predict in advance the form and approxi-
mate severity of the hemolytic process and as a consequence institute
treatment of the infant at an earlier date. In the infant, at birth, or
developing soon after birth, we find a jaundice, edema, hepatomegaly and
splenomegaly with a normoblastic picture in the blood and bone marrow
smears.

These evidences vary considerably with the different forms of the
disease mentioned above. At necropsy examination we find evidences
of a hyperplastic normoblastic bone marrow with foci of extra-medul-
lary hematopoiesis in the liver, spleen, and kidneys. Oftentimes in
the lungs we find hemocytoblasts in the pulmonary capillaries. In
some of the more severely affected infants there is evidence of kern-
icterus and usually evidences of enlargement of the liver and of the
spleen.

In hemolytic disease immediate transfusion with adequate amounts
of Rh negative blood is, at present, the treatment of choice. If Rh nega-
tive blood is used there is no hemolysis of the transfused blood by the

antibody in the infant. The infant is not breast fed because of the possibility of continued transfer of the Rh antibody from mother to infant in the breast milk. For the most part repeated small transfusions have been used quite successfully; however, Wiener has recommended massive replacement transfusions in which the infant is bled of his blood through an artery and at the same time blood from an Rh negative donor is given intravenously. The results of treatment by small transfusions in our most recent 18 cases of hemolytic disease may be seen in the following chart:

HEMOLYTIC DISEASE OF THE NEWBORN
(Summary of Recent Cases)

Cases	No.	Deaths
Icteric	16	2
Hydrops	1	0
Adm. from another hospital	1	1
Total	18	3

This is obviously a much lower mortality rate than we might anticipate without the benefit of immediate and adequate transfusions. In 16 of these 18 cases the transfusion data are summarized on the accompanying chart:

INTRA-OSSEOUS TRANSFUSION DATA
(16 cases)

Transfusions	56
No. per case (Aver.)	3.25
Cc. per case (Aver.)	188.5

We have used the intra-osseous as well as the umbilical route in our patients for convenience and ease of transfusion. For infants in whom hemolytic disease was anticipated we have been able to use the umbilical cord very successfully. With all of these facts in mind I would like to suggest the following policy in pregnant women with regard to the Rh factor.

SUGGESTED POLICY IN PREGNANCY

1. All obstetric patients are Rh typed at the time of first visit. In the Rh negative group also type husband, other children, and if possible the parents of husband. Do Hr typing on husband if available.

2. In all Rh negative females with Rh positive husbands do anti-RH and blocking tests at 2 week intervals beginning at 24th week of gestation and at 1 week intervals after 30 weeks gestation.

3. Have Rh negative blood available for immediate transfusion of all infants delivered of women with anti Rh or blocking antibodies.

4. In all women with Rh antibodies study the infant carefully at birth noting the size and weight of placenta, presence of hydramnios, color of amniotic fluid and repeated blood smears on infant.

If these various suggestions are followed it is entirely probable that hemolytic disease can be anticipated with some degree of certainty and adequate therapeutic steps carried out. I mention two more items not because they are of clinical importance at this time but because they may be theoretically important at a later date. If an individual is simultaneously injected with two antigens he will react almost entirely to the stronger of these two antigens. As a consequence it is theoretically possible to give during early pregnancy, a strong antigen and inhibit sensitization to the Rh factor. At present we are unable to predict which women are susceptible to Rh sensitization.

The second observation is based on the work of Homberger who has found in experimental animals immunized with rhesus cells that the simultaneous administration of sodium salicylate will inhibit the production of antibodies. It is impossible to use this drug at present because of the high toxicity of the drug but the observation is of importance because it is entirely possible that other chemical agents may be found which will inhibit the production of the Rh antibodies but will not have the high toxicity of large doses of sodium salicylate.

SUMMARY:

I have reviewed the recent literature concerning the Rh factor and its relationship to hemolytic disease of the newborn. As we study this problem more thoroughly we become impressed particularly with potential sensitization of young females by indiscriminate use of blood. It is probable that we should omit the use of intra-muscular blood, and Rh positive blood to Rh negative young female infants. When patients come to us worried because of incomplete information based on popular accounts of this subject in lay magazines we can assure them that not all women become sensitized equally and hence there is a strong probability that they will never deliver an infant with hemolytic disease even though the serologic sequence is consistent. Further, that if they should develop this form of sensitivity they will probably have several normal children before they have one with hemolytic disease, and if the father is heterozygous Rh positive 50% of the children will be born as Rh negative infants and hence free of hemolytic disease. If the infants are born with hemolytic disease and especially if this is anticipated, immediate prompt treatment improves the prognosis immeasurably and will result in normal living children even though they have hemolytic disease in infancy. Further work can be done along the line suggested by double immunization and the use of chemical reagents to diminish the capability of forming antibodies.

BIBLIOGRAPHY

1. Burnham, L.: The common etiology of erythroblastosis and transfusion accidents in pregnancy.
   Am. J. Ob. Gyn. 42:389-397 Sept. 1941.

2. Davidsohn, I.: Fetal erythroblastosis. J.A.M.A. 127:633-638, March 17, 1945.

3. Diamond, L. K., and Abelson, N. M.: The demonstration of anti-Rh agglutinins. An accurate and rapid slide test. J. Lab. & Clin. Med. 30:204-212, 1945.

4. Elston, J. T., Jaynes, R., Kaump, D. H., and Irwin, W. A.: Intraosseous infusions in infants and children. Am. J. Clin. Path. 17:143-150, Feb. 1947.

5. Homberger, F.: Sodium Salicylate inhibiting anti-Rh immunization in animals. Proc. Soc. Exp. Biol. & Med. 61:101-102, 1946.

6. Levine, P.: The pathogenesis of erythroblastosis fetalis.
   J. Ped. 23:656-675 Dec. 1943.

7. Levine, P.: Isoimmunization by the Rh factor—a new cause of fetal and neonatal morbidity.
   Human Fertility. 9:65-72 Sept. 1944.

8. Levine, P.: Prevention of unintentional isoimmunization of the Rh negative female population.
   J.A.M.A. 128:946 July 28, 1945.

9. Levine, P.: On the Hr factor and the Rh genetic theory.
   Science: 102:1-4 July 6, 1945.

10. Levine, P., Katzin, E. M. and Burnham, L.: Isoimmunization in pregnancy.
    J.A.M.A. 116:825-827 March 1, 1941.

11. Levine, P., Vogel, P., Katzin, E. M. and Burnham, L.: Pathogenesis of erythroblastosis fetalis: statistical evidence.
    Science: 94:371-372 Oct. 17, 1941.

12. Page, E. W., Hunt, M., and Lucia, S. P.: The antepartum prediction of hemolytic disease of the newborn.
    Am. J. Ob. Gyn. 52:794-796 Nov. 1946.

13. Texter, E. and Kaump, D. H.: Unpublished data.

14. Unger, L. J., Weinberg, M. and Lefkon, M.: The Rh factor as applied to the operation of blood banks.
    Am. J. Clin. Path. 16:498-505 Aug. 1946.

15. Wiener, A. S.: Recent advances in knowledge of the Rh blood factors with special reference to the clinical applications.
    Trans. Coll. Phy. of Phila. 13:105-122 Dec. 1945.

16. Wiener, A. S., and Peters, H. R.: Hemolytic reactions following transfusions of blood of the homologous group, with three cases in which the same agglutinogen was responsible.
    Ann. Int. Med. 13:2306-2322 June, 1940.