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Rh Disease...1970

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It is unusual that a disease entity can be predicted, recognized, defined, treated and finally prevented, all in one's lifetime. Such is the case, however, for Rh disease if you are old enough.

The prophetic statement of Dr. Theobold Smith in 1909, "Passive antibody mixed with antigen renders the antigen quite inactive as an immunizing agent," in no way predicted its practical application in 1968.

It was in 1940 that Landsteiner and Wiener discovered the Rh factor. Eight years earlier, Diamond and his associates, on the basis of clinical observations, rightly observed that hydrops fetalis, icterus gravis neonatorum and congenital anemia were all symptoms of the same clinical disease, which they labelled "erythroblastosis." There was then a period of clinical sparring in terminology - erythroblastosis vs. hemolytic disease of the newborn - causing great difficulties in interpreting newborn and stillbirth death certificates. Fortunately, most of these difficulties have been overcome by the refinement in diagnostic technics.

In 1940, it was found that injection of red blood cells of the rhesus monkey into rabbits produced a serum factor which caused the agglutination of monkey red cells. When tried with red blood cells of human beings, about 85% of individuals showed agglutination of red cells, while 15% did not. There was no sex difference. P. Levine and associates then cleared the way by pointing out that incompatible transfusions, or injections of incompatible intramuscular blood, caused sensitization. Although this incompatibility was important in males, it was especially important in females who were Rh negative, married to Rh positive males. Half or all of their offspring will be Rh positive, depending whether he has one or two genes for Rh positiveness. This state of affairs can best be carried out by the determination of Rh positiveness or negativeness in relatives. If an Rh negative woman happens to be lucky enough to marry an Rh negative man, she need have no worries from this source.

Rh determinations were first used to prevent mismatched transfusions. By 1945, it was learned that 10 to 12% of babies born alive to an Rh negative woman married to an Rh positive man were apt to be severely ill with anemia and post-natal jaundice which, if untreated, led to permanent mental damage including mental retardation, motor disability and even cerebral palsy. Autopsy showed kernicterus, yellow staining of the globus pallidus and other basilar nuclei. There were also many stillbirths of hydropic babies with a large spongy placenta. Polyhydramnios was frequent.

After a trial of intentional premature delivery of the infant to prevent intra-uterine death, exchange transfusion was instituted in 1947 to minimize post-natal jaundice and neonatal death. In general, when the infant's cord blood was shown to be Rh positive and the bilirubin level approached 20 mgs/100 cc whole blood in a full-term infant and 12 mgs in a premature baby, 250 to 500 cc of 0 neg, low titer A blood was injected into an infant via its umbilical vein in 10 cc doses after withdrawal of an equal amount of blood over a period of two hours or so. With increasing experience, the neonatal mortality rate of sensitized babies was reduced from 50% to 5%. A number of these umbilical vein catheterizations were, in fact, unwittingly intra-atrial transfusions, with the catheter passed through the ductus venosus, up the inferior vena cava, into the right atrium and through the foramen ovale into the left atrium, for it was a well known dictum among pediatric residents that "when the blood withdrawn is really pink, the exchange transfusion works very well."

The next advance came in the 1950's when Freda and others bravely performed amniocentesis to determine the bilirubin content of amniotic fluid. It had been obvious after years of experience that the mother's blood anti-D titers during the last trimester had little to do with the condition of the infant. Serial amniotic fluid bilirubin determinations resulted in a number of graphs which were useful in deciding when to do a premature induction of labor or a caesarian section to prevent an intra-uterine death from erythroblastosis.

In 1963, Liley added the last dramatic touch to treatment of erythroblastosis - intra-uterine transfusion - which reduced the fetal mortality from erythroblastosis from 100% to 60%. Now it appears that there is no need for further improvement in therapy, for complete prevention is at hand.

Shortly before 1950, Wiener had suggested a plausible mechanism of the sensitization of an Rh negative woman by her Rh positive baby - transplacental bleeding.

Even in the first trimester, it has been demonstrated that trophoblast cells can be found in maternal blood and, later, that atabrine-tagged maternal red cells can be found in the fetus. There finally is a consensus of opinion that at the time of delivery, a varying amount of fetal blood cells finds its way into the maternal intervillous space and veins draining the placenta as it separates from the uterine wall. Kleiauer devised a comparatively simple chemical test to quantitate the number of fetal cells which enter the mother's bloodstream. The basis is the difference between Hgb F and Hgb A. Some clinics take the trouble to determine the relative fetal-maternal transfusion after delivery, but most do not.

The elimination of Rh disease in infants and sensitization of their mothers began with the recognition that women incompatible with their infants in the ABO system often were protected from being sensitized by Rh imcompatibility. It seemed logical to develop an anti-Rh globulin. Men who were Rh negative were given Rh positive blood cells plus anti-Rh antibodies. None became sensitized, while those receiving Rh positive cells alone did.

No doubt, as public health specialists you are more interested in the present state of affairs than historical background.

About one in eight marriages involves one of an Rh negative woman and an Rh positive man. It is estimated that 2-300,000 women are at risk annually of being sensitized.

The estimated number of candidates depends on race and on previous isoimmunization either by a mismatched blood transfusion or intramuscular blood, or by an Rh positive baby. The expected number of white Americans of European descent and of Negroes are as follows:

	White		Negro	
A. Rh negative (r.r)	15%		6%	
B. Homozygous Rh positive (R,R)	37%		57%	
C. Heterozygous Rh positive (R,r)	48%		36%	
all A x B matings will be positive	.15 x .37 =	.0555	.06 x .57 =	.034
½ A x C matings will be positive	$\frac{.15 \times .48}{2}$ =	.0360	$\frac{.06 \times (36)}{2}$ =	.011
		.0915		.045
Minus previously immunized (.086x.0915)		.0079	(.086x.045)=	.004
		.0836		.041
	Or	8.4%		4.1%

The number of Orientals at risk is slightly less than that of Negroes.

Rh immune globulin was licensed in April 1968. A second vaccine is about to be licensed. Its use in susceptible women within 72 hours of the birth of an Rh positive baby, stillbirth or miscarriage is remarkably successful in preventing isoimmunization of the mother, as evidenced by her lack of antibodies and the health of the succeeding positive baby. Of course, its use is contraindicated in women already sensitized to the D antigen. Exchange or intrauterine transfusion will still be needed in their babies until the end of their reproductive period.

How many women who need this vaccine are receiving it? A survey of 99 maternity hospitals conducted by Mr. Stickle and myself, of The National Foundation, in December 1968 showed a 77% utilization in white women and a 61% utilization in non-white women.

What are the reasons for these low figures?

1. Cost. The original vaccine cost $65.00 a dose (300 micrograms of immune globulin). This figure is now down to $35.00 in the United States, while in Canada it has always been $10.00. Ideally, a number of laboratory tests should be performed before the vaccine is given to see if the mother's red cells are compatible with the vaccine, to see if she has no unusual rare antibodies, etc. etc. These tests often cost as much as the vaccine, if not more. In case of doubt as to the results of these tests, the advice of most hematologists is to give the vaccine anyway, since there seem to be no ill effects due to it. Thus, some hospitals are giving the vaccine intramuscularly to every Rh negative woman following miscarriage, ectopic pregnancy, stillbirth or live birth.

2. Objection to receiving blood products, such as by Jehovah's Witnesses.

3. Declaration by the woman that she will have no more pregnancies. It is unsafe to accept this statement unless sterilization is performed.

4. Resistance of the physician to introduce a new treatment and lack of education of the public to demand it. In our survey, it was mentioned frequently that the physician was unaware of the existence and benefits of this new vaccine. Often, his patient was the one who brought it to his attention.

As for meeting the cost of the vaccine, several avenues are hopeful. The cost of one dose is coming down as competition becomes keener. One state, Massachusetts, has enough vaccine prepared to cover all its needs, at $10.00 a dose, and is awaiting official approval of its product. The vaccine assistance act, passed by the Senate and now before the House, includes Rh vaccine. An increasing number of hospital insurance plans are including the cost of the vaccine and, occasionally, the laboratory work in their benefits.

It is obvious that blood grouping, at least of the ABO and Rh systems should be performed on premarital blood samples drawn for the diagnosis of syphilis. The presence of rubella antibodies also should be determined on this sample. Such a pilot project is under way in the New York City Health Department, assisted by The National Foundation-March of Dimes, although Diamond states that blood grouping was routine in Massachusetts on premarital blood samples in the early 1950's.

The risk of hepatitis from use of the vaccine is a logical question to ask. Gorman states that as of April 1, 1970, hepatitis has occurred following vaccination in not more than a dozen women. Some of these were in areas where hepatitis is endemic. A causal relation between administration of the vaccine and occurrence of hepatitis has not been established. Gammaglobulin as it is prepared for this vaccine has been shown to be remarkably free of the hepatitis virus.

Many aspects of the Rh problem have not been covered because of time limitations. It would be wishful thinking to state that the Rh problem will soon be a thing of the past. As Liley points out, the negative allele, which in due time will disappear, will now persist. By diligent and conscientious effort, we can keep hemolytic disease subdued.

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