I shall review some of the important steps by which Rh disease arose as a concept, evolved as a well-defined disease and, subsequently, was conquered. As I describe this "rise and fall," there will appear the thread of another theme, namely the role of science in the study of clinical medicine as well as in the eradication of disease.

The story of Rh disease, when told, usually begins with the momentous discoveries of Philip Levine and Alexander Weiner, both of New York City. But, as in all other scientific discoveries, much work on this problem paved the way for their observations. In 1938, Dr. Ruth Darrow of the Women's and Children's Hospital of Chicago, published a remarkable and detailed analysis of the condition "Icterus Gravis (Erythroblastosis) Neonatorum."[1] Her personal dedication to this disease because of her own problem with Rh disease is dramatically described in Zimmerman's excellent history of "Rh."[2] Her paper, a critical and brilliant analysis of the literature, included case descriptions by clinicians and experiments and observations by medical scientists.

She reasoned, on the basis of available family studies, that the mother was a constant factor; in other words, an offspring of the same mother tended to have the disease rather than an offspring of the same father. She observed that the first child was seldom afflicted and that the mother herself was not affected. Dr. Darrow concluded from these observations that the disease is an acquired one and that the
mother develops a material in her blood that causes no harm to her but is transmitted through the placenta to the fetus. Since the disease, as analyzed by the many who preceded her, was one of red blood cells, she logically concluded that the destruction of these cells had occurred by some form of "immune reaction." She reasoned further that the mother had become actively immunized against these cells and that the antibodies so formed might then pass to the child through the placenta. Thus, by critical analysis of published clinical observations and experiments, she arrived at an almost complete description of the nature of the disease and, in her concluding line, she stated that "Antigen-antibody reaction seems to explain best all aspects of these related disorders."

Dr. Darrow's analysis of the problem stopped short, however, of recognizing that the antigen causing the disease was, in fact, a blood group antigen. She states, "This mechanism, incidentally, bears no relation to a difference in blood groups of mother and child." Had she fully appreciated the ever present limitation of medical knowledge, she might have stated simply, "No known difference in blood groups." Dr. Darrow assumed that the disease was due to an antibody against hemoglobin F which, at that time, was the only known difference between the red cells of newborns and those of adults.

A total of 81 references were included in her article, some to articles published in the early years of the century. The number of publications became more frequent up to the time of her review. Thus much detailed and careful scientific study had been performed by clinicians and scientists and this led to the development of sufficient knowledge to permit the rapid fruition of subsequent discoveries.

In 1939, Dr. Philip Levine published the first of his historic papers on hemolytic disease of the newborn infant.[3] It is interesting to consider the case described in that paper, in terms of how medicine functioned at that time. A 25 year old woman in her second pregnancy was delivered of a macerated stillborn fetus. Because of bleeding, she received a transfusion from her husband who was Group O, like herself. She suffered a transfusion reaction and because of that her blood was studied by the "Blood Transfusion Betterment Association." I like the title of that association because it expresses so well for me social activism in medicine, a quality that I have described previously[4] as one of the best of medicine and medical science. Studies of that "Association" permitted them to select six compatible donors and the transfusions were then uneventful and the patient recovered.

Presumably there was much discussion about this case by clinicians concerned about the nature of unknown problems in their patients. Such concern and study about the nature of clinical phenomena is, in my opinion, a major component of medical research and it is one which appears to have faded in recent years.[4]

A sample of serum was sent to Dr. Philip Levine for analysis. He was able to show that the serum reacted with the blood of the father and with about 80% of other subjects. Dr. Levine reasoned that "Presumably, the immunizing property in the blood or tissues of the fetus must have been inherited from the father." This postulate was, of course, a major one, because it suggested that a mother could be immunized by her fetus and that this represented a second method of immunization other than that caused by a blood transfusion. He did not, at that time, ascribe the death of the fetus to the disease but
rather thought that the dead fetus in utero might permit tissues such as red cells to pass into the mother and thereby cause immunization. The significant contribution of this paper was the concept that the fetus could immunize the mother.

In 1940, the year after the publication of Levine's paper on hemolytic disease of the newborn, Dr. Alexander Weiner, working with Dr. Karl Landsteiner, described experiments in which red cells of rhesus monkeys were injected into a rabbit who produced an antibody which reacted with red cells of about 80% of humans. The antigen in the monkey blood was referred to as the rhesus or Rh factor. The next paper by Weiner was a momentous one, in my opinion, and its historic importance is well analyzed by Clarke. In that paper, Weiner and his colleague, Peters, describe three transfusion reactions which occurred in donor-recipient combinations of the same ABO type. These "intra-group" reactions had been known for many years. In fact, Weiner and Peters cite many reports dating back to 1933. Other scientists and physicians concerned about the problem of intra-group reactions had studied the phenomena but, in their paper, Weiner and Peters were able to show that the antibodies in these subjects reacted with the donor cells and indeed with the red cells of about 80% of normal subjects. Furthermore, the antibodies showed complete identity with the antibody previously described in rats immunized by rhesus cells. They concluded, therefore, that the antibody responsible for these transfusion reactions was an antibody reactive against the Rh factor. Weiner and Peters speak for the first time of anti-Rh antibodies and conclude, "Following the appearance of the anti-Rh agglutinins, the transfusion of Rh-positive blood gave rise to hemolytic reactions." This crucial insight opened an entirely new era in transfusion therapy and in blood group serology.

Weiner and Peters made the interesting observation, again built on the information accumulated in previous years, that most other intra-group reactions in which a patient had never received a transfusion previously occurred in women! They considered that observation to be further support for the postulate of Levine and Stetson that immunization in these cases had occurred by antigenic stimulation from the fetus. It is of historic interest that, in the paper of Weiner and Peters, they not only reviewed the history of intra-group reactions previously reported, but they also tested the antibodies in some of those cases and proved that they were indeed anti-Rh antibodies. Levine and Weiner were in the same city and presumably knew much of each other's work, yet Weiner did not test the serum of Levine's patient. It would seem, however, that the work was being done by Levine because, in the next year, Levine published his paper which included such studies and which led to the definitive description of the nature of Rh disease.

In their article, Levine et al. described virtually all the features of Rh disease which we now recognize. The summary of that paper contains a brilliant, comprehensive analysis of the nature of Rh disease. That summary follows:

1. In 93% of the cases investigated, erythroblastosis fetalis results from the iso-immunization of the Rh negative mother by the Rh factor in the red blood cells of the fetus.
2. In the remaining cases, blood factors other than Rh are responsible for the iso-immunization.
3. Agglutination tests for the Rh factor are of value as a laboratory aid in the diagnosis of
4. The pathologic manifestations of this disease are produced by the intrauterine action of maternal immune agglutinins on the susceptible red blood cells of the fetus.

5. It is probable that iso-immunization is also the cause of a certain proportion of habitual abortions and stillbirths.

6. Intra-group transfusion accidents associated with pregnancy can now be prevented by the use of Rh negative donors and by means of a modified cross-matching test.

Thus, within two years of apparently furious activity in New York City, the work of Levine and Weiner resulted in a complete description of the nature of Rh disease. The rivalry for credit between these two scientists is well known. Clearly, both of their contributions were enormous and, together with the work that preceded them, led to the discovery of Rh disease.

Following these historic developments in the early 1940s, there were many developments in the diagnosis and treatment of this disease which themselves were outstanding advances in medicine. These included the study of blood group inheritance, the development of the Coombs test, the concept of exchange transfusion, the use of amniotic fluid for diagnosis and the development of intrauterine transfusion. These were tremendous achievements which, by the 1960s, were so fully developed, that the disease could be accurately diagnosed and treated as it is today. I wish now to move from this point to those steps which appear to be leading to the eradication of the disease. Once again, this had involved the work of many physicians who pursued the problems scientifically by clinical observation, laboratory methodology, experimental design and theoretical analysis.

An important series of observations was reported by Nevanlinna and Vainio of Finland. Dr. Nevanlinna, the son of a famous Finnish mathematician, brought to the study of Rh disease an approach which reflects his background. In that study they concluded that ABO incompatibility in the mother and fetus (for example, where the baby was blood group A and the mother blood group O) protected the mother from being immunized. The protection was limited to the pregnancy that resulted in iso-immunization and not to later pregnancies. The thesis that developed, therefore, was that the anti-A of the O mother destroyed the A Rh-positive cells of the fetus before they could produce immunization of the Rh-negative mother. The hypothesis developed in that analysis of the natural history of Rh immunization was supported by the observations of Stern et al. who showed that ABO incompatible Rh-positive erythrocytes injected into Rh-negative men were much less likely to induce formation of Rh antibodies than ABO compatible Rh-positive cells. It was their interpretation that the antigenicity of Rh-positive blood cells could be altered as a result of the action of antibodies on those cells. This was a most important hypothesis and received further support from a subsequent article by Stern and Berger. They reported that Rh-positive ABO compatible red cells coated with antiRh antibodies failed to produce immunization. The observation that antibodies against red blood cells could alter their antigenicity heralded the methods developed subsequently for the prevention of Rh immunization and thereby the eradication of the disease.

The successful prevention of Rh immunization also resulted from the work of clinicians and basic
scientists who steadily built the foundation upon which the technique of prevention was created. As noted above, both Levine and Weiner felt that immunization of the mother resulted from the passage of fetal erythrocytes into the maternal circulation. However, it remained to be proved that such a phenomenon could occur. Bruce Chown of Winnipeg studied a case of unexplained anemia in a newborn infant and proved that hemorrhage of fetal erythrocytes could enter the maternal circulation! It seemed unlikely, however, that this massive type of hemorrhage could be an explanation for the immunizing events that Levine, Nevanlinna and others had postulated. It was more likely that small hemorrhages (insufficient to cause fetal anemia) occurred frequently. To prove that these small hemorrhages occurred required a technique for demonstrating minute quantities of fetal erythrocytes in the maternal circulation. The work of Drs. Kleihauer and Betke in Freiburg, Germany, provided this technique. Dr. Kleihauer was a young, pediatric hematologist working in Dr. Betke's laboratory, where Dr. Betke himself had been studying fetal hemoglobin for many years. Kleihauer and Betke developed a technique which distinguished fetal erythrocytes from adult erythrocytes on a stained blood smear. The technique was extremely sensitive and permitted the identification of one drop of fetal blood in the entire circulation of a mother.

Using this technique, it became evident that fetal erythrocytes frequently enter the maternal circulation throughout most of pregnancy. The volumes found usually are approximately 0.1 ml and these quantities of Rh-positive fetal erythrocytes were demonstrated to be sufficient to produce immunization. Increased bleeding tends to occur more frequently towards the end of the pregnancy, however, maternal immunization occurred because of transplacental hemorrhage of small quantities (approximately 0.1 ml) of fetal erythrocytes.[13]

Clearly, Rh-negative women bearing Rh-positive fetuses were being "transfused" repeatedly with Rh-positive erythrocytes. The stage was set! Could that process of Rh immunization be prevented? If so, Rh disease would be eradicated.

The means of preventing Rh immunization resulted from the work of Drs. Ron Finn, Cyril Clarke and their colleagues in the University of Liverpool[14] and of Drs. Vince Freda and John Gorman of Columbia University working with Dr. Bill Pollack of the Ortho Research Foundation.[15] The Liverpool group reasoned that since anti-A antibodies appeared to prevent Rh immunization by Rh positive erythrocytes (see the work of Nevanlinna and Stern cited above), that it was possible that the administration of anti-Rh antibodies to the Rh-negative mother also might prevent immunization by the Rh-positive cells, presumably by destroying them. The New York group recalled the studies of Smith[16] in the early part of the century who pointed out that active immunization by a given antigen could be prevented if the individual was given antibodies to that antigen at the same time. Both groups reasoned also that since antibodies rarely occurred during a first pregnancy (the antibodies appeared months after delivery), prevention might be successful if carried out postpartum. Further support for this approach was their belief that antigenically significant quantities of fetal erythrocytes were found in the maternal circulation only at or around the time of delivery. Although the truth of that assumption is questionable, the success of their approach is beyond doubt.
The plan, therefore, was to inject anti-Rh (anti-D) gamma globulin postpartum. For convenience and safety, this was prepared as a gamma globulin concentrate. Clinical trials then ensued in Liverpool and New York. A most recent compilation[17] of these trials, as well as those of others that were conducted elsewhere in the world, shows that of 75,075 women treated, only 184 (0.25%) developed antibodies during the first six months postpartum, compared to at least 3,904 (5.2%) expected. The disease has been almost completely eradicated.

There is still concern about the residual group of immunized women. A major cause of immunization is failure to administer anti-Rh gamma globulin. Even when compliance is 100%, it would appear that in some women (in some series, 1-2%),[17] immunization develops before delivery, hence postpartum administration of anti-Rh gamma globulin would be of no value. Antepartum immunization is a problem which can be prevented in most instances by a prophylactic injection of anti-Rh gamma globulin at the 28th week of gestation.[17] The value of such therapy, however, is controversial because so many additional injections of anti-Rh gamma globulin (more than double that now employed) would be required to prevent immunization in 1% of Rh-negative women. Cost effectiveness studies which have been employed[17] suggest that it is a valuable procedure. There is, however,[17] opposition to this approach by those who believe the cost of antepartum protection is too great to be borne by society.[17] As a result, Rh immunization may continue to occur in a small proportion of women in countries which do not provide antepartum protection. The eradication of Rh disease may stop slightly short of completion, at least in some countries, because of economic limitations.

This, then, is some of the history of Rh disease as I see it. Levine and Weiner made the monumental discoveries that opened this field; however, even their work developed on the knowledge base of the medicine and science that preceded it. Their work was followed by the rapid development of techniques of diagnosis and treatment which made possible the successful treatment of babies with Rh disease. On that base of understanding the nature of the disease, the Liverpool and New York groups developed their great studies leading to the eradication of the disease. "The rise and fall" of Rh disease is a story of the work of scholars of medicine, caring for and observing their patients, testing blood samples in laboratories, analyzing a heterogeneous accumulation of data and observations, evolving theories, designing clinical trials and always pursuing their programs, so that they would most efficiently benefit all patients. Hence, scholarship and social activism have produced the best that medicine has to offer. I have written previously[4] about the relationship between basic science and clinical medicine. The story of Rh disease teaches us that these two dimensions of medicine, working together, lead to the best in patient care and provide the means for understanding and conquering human disease.

REFERENCES


