THE RHESUS FACTOR

(25th ANNIVERSARY)

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This year we celebrate the 25th anniversary of the publication by Landsteiner and Wiener of a paper in which the discovery of the Rhesus factor was first announced. As this, with the sole exception of the ABO blood groups, was the most important discovery in the field, it seems right that we recall the event at this time.

The circumstances which led up to the discovery of the Rhesus factor were as follows: During the 1930s Landsteiner and Wiener were investigating the evolution of the M agglutinogen. In the course of their experiments they injected rabbits with the red blood cells of Rhesus monkeys and after suitable absorption succeeded in obtaining an anti-M reagent which served their purpose. With this they explored the anatomy of the M agglutinogen.

It then occurred to them that other, unknown, factors in human blood might be discovered by this approach. They therefore removed the anti-M agglutinins in their rabbits' sera and tested the residual reagent against the red cells of human beings. The results were astounding. They found that their reagent would agglutinate the cells of 85% of white people and that it failed to agglutinate the cells of the remaining 15%. Those that agglutinated were said to be Rhesus positive, while those that did not were Rhesus negative.

This division of the population into Rhesus positive and Rhesus negative groups is now known to be the most important division outside the ABO blood groups, but in those early days (it was only 1937) the Rhesus factor and its distribution was of academic interest only. It was some time before the practical importance of the discovery was realized.

Then, in 1939, Wiener and Peters investigated cases where recipients of blood transfusions had severe (one was fatal) haemolytic reactions. This was not such an exceptionally rare occurrence in those days, but what made these particular cases unusually interesting was that each had received his own ABO blood group. In the course of the investigation the sera of the patients were tested and in each case an irregular antibody was found. Further testing showed that this antibody agglutinated the cells of 85% of the population and that it failed to agglutinate the cells of the remaining 15%. In other words it gave results parallel with those of the rabbits' sera. Still further testing showed that all the patients were Rhesus negative while the offending donor blood was Rhesus positive. Thus the Rhesus factor was implicated as the main cause of those haemolytic transfusions which occurred when the correct ABO blood group was given. In this way a discovery which at first seemed to have no practical application, was, within 3 years, shown to be of fundamental importance in blood transfusion.

It was at this stage that Landsteiner and Wiener[1] announced the discovery they had made 3 years previously; and Wiener and Peters[2] described its importance in blood transfusion. The year was 1940; the war in Europe had already begun; blood transfusion would soon be sorely needed. But there was more to follow. Levine discovered an irregular antibody in the sera of women who had given birth to erythroblastotic babies. This discovery was made when these mothers had severe reactions when transfused with what appeared to be the correct blood. When tested with anti-Rhesus serum, however, they proved to be Rhesus negative in the majority of cases. So it looked as though the Rhesus factor was implicated here too. But there was one great difficulty; their sera did not agglutinate the red cells of 85% of the population. This difficulty was resolved by Dr. Wiener who, in a series of brilliant experiments showed that Rhesus antibodies can exist in two forms, one which agglutinates cells in saline media, and one which does not. The latter he called 'univalent antibodies' and when tested in the correct way these too agglutinate the red cells of 85% of the population. Furthermore he showed that it is these univalent antibodies, which, by crossing the placenta, cause erythroblastosis in the unborn child.

Thus the enigma of erythroblastosis was resolved and thus also a second role of importance was assigned to the Rhesus factor, the discovery of which now ranks with the great discoveries in the history of medicine.

But complications were soon to follow. It was found that there were a number of factors related to the Rhesus factor and that some of these factors were reciprocally related to each other. This reciprocal relationship recalls the situation which obtains in the MN system of blood groups. In itself it was nothing new but it was responsible, in the hands of British workers, for the revival of an old theory of Rhesus inheritance. This theory had already been considered and rejected by Wiener, but now it was being revived, and with it a new system of nomenclature was devised which was tailored to fit the theory.

The new nomenclature, variously called the British or CDE nomenclature, looked simple and because of this it became extraordinarily popular, not only throughout Britain, but also in America. It is by far the most commonly used nomenclature in scientific papers and in medical textbooks. That it does not reflect the facts of the serological reactions or the facts of Rhesus inheritance is an extraordinary thing. Even more extraordinary is its wide acceptance in view of the positive misinformation which it implies.

Wiener's nomenclature, on the other hand, is ingenious and simple; it is imaginative but not fanciful. The situation, as he explains it, is that every human being receives a single Rhesus gene from each parent. Each of these genes determines a Rhesus agglutinogen and each agglutinogen possesses an indefinite number of blood factors. An example may make this clear. The Rhesus gene R' determines the agglutinogen Rh_1 and this agglutinogen possesses a number of factors including **Rh_o**, **rh′**, **hr″**, **Rh^A**, **Rh^B**, **Rh^C**, **Rh^D**, **Hr**, **hr^s**, etc., and as time goes on no doubt others will be added to the list. Thus we see how a single gene determines a single agglutinogen which possesses multiple factors.

None but those concerned with immunohaematology need become involved in the details of the structure of the agglutinogen, but all practitioners should know that a group designated with a large R (e.g. Rh_1, Rh_2, Rh_o, Rh_z) is Rhesus positive, while a group designated with a small r (e.g. rh, rh′, rh″, rh_y) is Rhesus negative.

The growth of our knowledge of the Rhesus system in the past 25 years has been tremendous. Dr. Wiener predicted that further Rhesus factors would be discovered and his prediction has come true. Of particular interest to South African doctors is the discovery by Dr. M. Shapiro, of Johannesburg, of the Rhesus factor which is now called **hr^s**. This discovery was made possible by an antibody which he found in the blood of a Bantu woman, Mrs. Shabalala. Her initial is now firmly established in medical literature. Shortly afterwards Dr. Grob-

belaar of Durban discovered an identical antibody in the blood of another Bantu woman, Mrs. Sakwe. There are now known to be 4 such cases in the world, 2 in South Africa and 2 in America. In the meantime Dr. Wiener continues to describe yet other new Rhesus factors.

Where will it all end? Wiener says that the end is not in sight. Yet all these complexities must not be allowed to dishearten the man charged with the management of placenta praevia, obstructed labour, and the other dramatic events of medical practice. If the simple rules which govern antenatal care and blood transfusion are known and observed then the requirements of first class practice will be satisfied.

REFERENCES

1. Landsteiner, K. and Wiener, A. S. (1940): Proc. Soc. Exp. Biol. (N.Y.), **113**, 223.
2. Wiener, A. S. and Peters, H. R. (1940): Ann. Intern. Med., **13**, 2306.