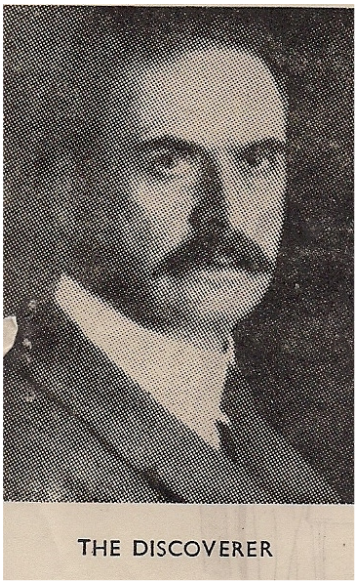
INTRODUCTORY NOTES

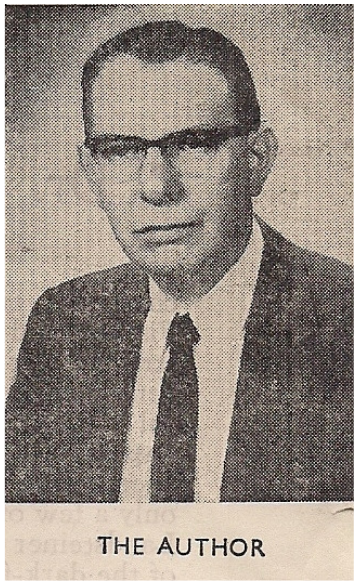
I have had a photocopy of an article called 'Dr Landsteiner: His work and the Rh Factor' by Dr A.S. Wiener M.D.' that was published in the journal Rakt Daan (i.e. Blood Donation) in my records for many years. Apart from the page numbers (i.e. pages 4-8) the copy gives no indication as to a publication reference or date [though the content would suggest that it was written in 1951-2]. I have been unable to locate a version of this article or journal via the Internet. Given the author and the topic I believe that this article is of historical interest and therefore a transcript of it is reproduced here as written; which is in two parts that were published consecutively, together with the photographs of Landsteiner and Wiener it contains. The article gives an historical insight into the work carried out by Landsteiner and Wiener, especially in the early work relating the MN and Rh blood groups. Note: The Passano Foundation Award for 1951 referred to in the text was made jointly to Philip Levine and Alexander Solomon Wiener.

Dr. LANDSTEINER: HIS WORK AND Rh FACTOR

Dr A.S. Wiener, M.D.



THE DISCOVERER



THE AUTHOR

PART ONE

The news that I had been selected to share the Passano Foundation Award for 1951 aroused mixed emotions in me. Naturally, I felt both happy and proud to learn that the work carried out by me, with the help of many associates, had been considered worthy of this honor, but I could not help feeling sad, realising that Dr. Karl

Landsteiner, who played such an important role in the early history of the Rh factor, is not alive to receive his due recognition.

It is now 22 years since I first met Dr. Landsteiner. The events leading up to this meeting began during the summer of 1928, when having completed my sophomore year at medical school I searched for a worth-while project on which to spend my vacations months. At that time, it had just been announced – incorrectly, as we now know – that incompatibility between the blood groups of mother and fetus was the cause of eclampsia. Dr. Silik H. Polayes was investigating this claim at the Jewish Hospital of Brooklyn, and kindly permitted me to assist him with the project.

At that time, knowledge regarding the blood groups was restricted to the four A-B-O groups and the sub-groups of A, but even that limited information was in a worse state of confusion than the far more complicated field of the Rh-Hr types today. There were 3 competing nomenclatures in general use, while 3 contrasting genetic theories each had their advocates. Though up to that time I had had no formal training in genetics, it was that aspect of the subject which appealed to me. I had always liked problems mathematical, and while receiving my premedical training at Cornell, had taken such courses as Advanced Calculus, Theory of Numbers, Vector Analysis and even Einstein's Theory, merely as a mental exercise and without thought of any practical application. When here at last I found a branch of medicine susceptible to exact mathematical treatment, I became intrigued, and devoured every text on genetics that I could lay my hands on. As a result, in the fall of 1928, I composed a purely theoretical mathematical analysis of the genetic theories of the blood groups, which yielded evidence supporting the theory of multiple allelic genes.

Unfortunately – or fortunately, as it later turned out – I had not been as careful in the introduction when discussing the discovery of the blood groups as in the remainder of the paper, and a few days after I had proudly surveyed this first publication of mine, a telephone call from Dr. Philip Levine announced that Dr. Karl Landsteiner wished to see me. One can well imagine the awe and trepidation with which I approached this interview at which a stripling medical student was to meet Karl Landsteiner of World renown. It turned out that with the gullibility of youth, I had quoted the assertion of a Japanese author that isoagglutination was in vogue in China and Japan as early as the 12th century. When I met Dr. Landsteiner I found that despite an impressive and stern demeanor, he was really a kindly and helpful scientist who gently suggested to me to investigate the source of the claim. A volume was then obtained from the Army Medical Library in Washington, containing ancient Chinese and Japanese folklore. According to this book, any person claiming to be an heir to an estate was subjected to the following test: His finger was pricked and a drop of his blood permitted to drip onto the dead person's skeleton; if the blood soaked into the bones, he was indeed their heir, otherwise he was an imposter. In a 2nd test to determine whether 2 individuals were relatives, drops of their blood were allowed to fall into a basin of water – if the drops came together, they were indeed related; if the drops flowed apart, they were not. This early experience taught me not only the obvious lesson to consult all original sources myself, but also to be critical of claims of highly implausible phenomena. It is one of the earmarks of the credulous and unreliable investigator that in his very first attempt he claims to have made some fantastic discovery or describes an effect that is highly improbable a priori. As a recent such example, I might cite the article published only a few months ago in an outstanding scientific Journal, claiming the ability to determine a person's blood group and sub-group by a clot of his blood plasma. In the same category belong other reports, such as the claim that so-called "Rh-hapten" can prevent or cure erythroblastosis.

When I first met Dr. Landsteiner, he had been in this Country as a member of the Rockefeller Institute for only seven years. He had a long record of fundamental discoveries behind him. In 1900, near the beginning of his career, he had already discovered the phenomenon of isoagglutination and the blood groups. Previously it had been believed that all human blood was alike, and even that there were no fundamental differences between human and animal blood. In fact, the first transfusions to man were carried out with lamb blood, and the objection raised to the use of lamb blood was not that it was harmful or dangerous, but that it was not proper to bring a lamb into the operating theatre, and that such transfusions might cause a patient to bleat and grow wool. Landois showed that if dogs are exsanguinated, their lives could be saved by replacing their blood with blood from other dogs, but that if blood from a different animal was introduced the dog recovered at first only to die a few days later. It was then found that blood serum had the capacity to clump or dissolve red cells from animals of another species, and therefore only human blood was used for transfusions. Despite this, dangerous reactions continued to occur after the rare transfusions that were attempted in those days. Landsteiner immediately realised that his discovery not only explained these reactions but provided a means of preventing them, but the application of his finding had to await the perfection of the technique of blood transfusion. It was not until a decade later that methods were devised for avoiding coagulation of blood during transfusion; blood transfusions then came into more general use and the value of blood grouping and cross-matching became evident. Following World War 1, blood transfusion became a regular hospital procedure and then the importance of Dr. Landsteiner's discovery began to be appreciated.

In the meantime, Dr. Landsteiner busied himself with such fundamental problems as the basis for the remarkable specificity of immune reactions. Why, he asked, when a person was infected with small-pox, for example, and recovered, did he produce antibodies which protected him against another attack of small-pox but not another disease? And why, when rabbits are immunized with horse serum, do they produce precipitins which react only with horse serum and no other blood serum, even from related species such as cattle, pigs or goats. Incidentally, in this way immunologists have been able to solve problems which even at the present time defy the chemists. On occasion, in this way we have been able to help the New York City Department of Health prove that certain butchers were diluting their ground beef with significant amounts of horse meat.

To solve this problem, Landsteiner made good use of his early chemical training with Emil Fisher, and succeeded in demonstrating that the specificity of antigens is dependant on their chemical structure, thus founding the important science of immuno-chemistry. To mention briefly only a few of his other discoveries, Landsteiner introduced the use of the dark-field microscope for the diagnosis of primary syphilis, and devised a fundamental modification of the Wasserman test that is the basis of the present day test. With Donath, he elucidated the mechanism of paroxysmal hemoglobinuria and devised a simple test for that disorder, whilst with Popper he transmitted poliomyelitis to rhesus monkeys for the first time, thus initiating the experimental study of that disease. This work, done in Vienna, was interrupted by the war. Realising that Austria held no certain future for him, Landsteiner then found a modest position in Holland. There, despite the interference of burdensome routine duties he continued his research work and published several important papers in the Dutch language, which he had learned in his few years there. Finally, in 1921, he came to this country with his wife and son upon invitation of the Rockefeller Institute. Here at last, he was given an adequate laboratory where he could work without the distraction of routine duties or the need of earning a livelihood. Within a relatively short period of time, he mastered the English language and

became an American Citizen, and during his remaining 22 years doubled his scientific contributions, which number more than 360 in all.

Landsteiner had always conceived of and individuality of human blood somewhat comparable to the finger-prints, and when he came to New York, he was able to resume his studies on the blood groups. Soon after my first visit to him, I read with great interest his report with Philip Levine of their discovery of the M.N.-types and the P agglutinogen and their heredity. I determined to investigate this subject, and Dr. Landsteiner kindly provided me with serum and advice to help the project along.

PART TWO

Thus began a close friendship which continued until the time of his death 15 years later. In the meantime, long delayed recognition had come to Landsteiner – in 1930 he travelled to Sweden to receive the Nobel Prize for the discovery of the blood groups made 30 years previously. About this time, I decided to undertake the preparation of a book on blood groups, and here again I received unexpected and generous help and encouragement from Dr. Karl Landsteiner. One evening a week was set aside for a regular visit to his home, and this continued for more than a decade. At these meetings I not only had the advantage of his invaluable constructive criticisms of my manuscript materials, but also the opportunity to learn at first hand from this great scientist his latest work and ideas, thus gaining an insight into the subject that stood me in good stead in later years when studying the serology and genetics of the Rh-Hr types. Thos pleasant meetings, the interludes during which we chatted of lighter matters, such as the scientist who had twins, baptised one of them and kept the other as a control, the visit to Dr. Landsteiner's summer homes in Nantucket and Newfane where we poured over galley proofs and page proofs together, are fond memories which will remain with me for the rest of my days.

It was first the medico-legal application and later the anthropological applications of blood groups that led to the joint study by Dr. Landsteiner and myself on blood factors in rhesus monkeys and the discovery of the Rh factor. As early as 1903, Landsteiner and Richter had demonstrated the feasibility of grouping dried human blood stains, and pointed out the usefulness of such tests in murder and assault cases. When the heredity of the blood groups was established, the second important medico-legal application in cases of disputed parentage became apparent. In both cases the tests are of negative value only – one may succeed in proving that a blood stain does not contain the victim's blood as when the blood groups are different: it is never possible to establish that stains contain the blood of a specified person. Similarly blood tests may prove that a certain man is not the father of a certain child, but cannot be used to prove that a man actually is the father. A falsely accused man had one chance in six of being cleared by the original four blood groups: the M-N types increased this chance to one in three: whilst the addition of the Rh-Hr types increased chances to more than 50%.

The interest of legislators in blood tests was stimulated by the notorious Chicago case in 1930, when two newborn babies were interchanged in the hospital. On arriving home from the hospital Mr. and Mrs. B found an adhesive label on their baby's back with the name "W", whilst Mr. and Mrs. "W's baby had been labelled "B". The first couple both belonged to group O whilst the baby at their home belonged to group A; on the other hand, in the other family, the father proved to be group AB, the mother group O and the baby group O. This double conflict with the laws of heredity was corrected by interchanging the babies and restoring them to their rightful

patents. More recently a similar case in Switzerland which could not be solved with the A-B-O or M-N tests was resolved by the Rh-Hr tests.

In 1935, with the advice of my lawyer father, bills were introduced into the New York State Legislature, and laws later passed giving the courts the power to order individuals to submit to blood tests in paternity disputes; later similar laws were passed which enable courts to compel defendants in assault and murder cases to submit to blood tests. Shortly after, the Office of the Chief Medical Examiner of New York City decided to open a laboratory for blood grouping tests for use in homicide cases, and I was appointed to direct the department. Aside from the interesting nature of the work, the position provided an opportunity to continue the research on blood groups.

One of the first projects that I undertook was to study the evolution of the agglutinogen M in monkeys and apes. When our preliminary results proved interesting, Dr. Landsteiner joined the project and from then on played the leading role in its development. It is necessary to acknowledge the generous support in the form of grant given to this work and to the later studies on the Rh factor by the American Medical Association and the United Hospital Fund of New York. The work was made possible also through the co-operation of Captain Cheyne Stout, who was Director of the Zoo in those days, and I well remember my first visit to him while he was convalescing from 3 long, deep, infected gashes in his back produced by one of the tigers.

It seems that after a party he had brought his friend to the Zoo and entered the tiger's cage in order to demonstrate his psychological powers of control over dumb beasts. After that visit, I was glad that my own studies were to be confined to the somewhat more tractable members of the primate order of mammals. My own only casualty occurred when a chimpanzee whom I had just bled retaliated by hitting me on the back of my neck with some of his saliva which had accurately projected across the room.

The laboratory of the Medical Examiner's Office was not far from Dr. Landsteiner's laboratory at the Rockefeller Institute, and during the next few years I travelled regularly between the two. Blood which I collected from monkeys and apes was tested by us both in our respective laboratories, while Dr. Landsteiner carried out most of the immunization experiments. When our findings proved that the agglutinogen M had a step-like evolution from monkeys to apes to man, it occurred to us that it should be possible to produce anti-M sera by immunizing rabbits with monkey blood. Rhesus blood was used for the experiment, and we found that anti-M sera could indeed be produced in that way. Continuing the experiments, in the hope of discovering new human blood types, we obtained some sera which clumped 85 percent of human bloods and which we designated as Rh positive, but failed to clump 15 percent which we designated Rh negative. We did not report these findings right away, because we wanted to improve the method of preparing the typing sera.

In the meantime, the transfusion of blood had become simplified by the use of citrate and the introduction of blood banks. Blood transfusions which formally were a rare procedure were now given by the thousands, and it became apparent that occasionally dangerous reactions could occur even though patient and donor both belonged to the same blood group. Dr. H. Raymond Peters consulted me regarding 2 such cases which had occurred in Baltimore, and in both these cases, as well as one of my own the patients proved to be Rh negative and sensitized to the Rh factor while the donors were Rh positive. The finding the Rh sensitization could give rise to

dangerous transfusion reactions stimulated Dr. Landsteiner and me to announce our discovery of the rhesus factor in January, 1940.

In parallel studies carried out at about the same time, Dr. Philip Levine and his collaborators developed the thesis of the isosensitization of the mother by the red cells of the fetus in utero, and showed how this could lead to intra-group transfusion reactions. Moreover, he showed how the maternal antibodies passing into the fetal circulation could cause stillbirths, or babies to have the blood disease known by the name erythroblastosis fetalis. Following the discovery of the Rh factor, he succeeded in identifying the antigen causing the sensitization and the corresponding maternal antibody with the rhesus antigen and antibody studied by Dr. Landsteiner and myself.

The subsequent development of the subject into a complex field with manifold applications is well known. There is not enough time to discuss such important matters as Rh blocking antibodies, the Rh-Hr types determined by the factors Rh_o, $rh^{/}$, $rh^{//}$, $hr^{/}$, $hr^{//}$, etc., and their heredity, or the treatment of erythroblastosis by exchange transfusion. The complicated system of Rh-Hr types has found practical applications not only in clinical medicine, but also in legal medicine, and in anthropology for the classification of human races. In England and America studies on the blood groups have advanced so far that 20 different agglutinogens from more than 8 independent blood group systems have been identified, giving rise to thousands of different types of human blood. Too bad that Dr. Landsteiner could not live to see his prediction fulfilled that blood group studies could disclose an individuality of the blood comparable to the fingerprints.

In conclusion, I would like to thank the many physicians who have indicated their appreciation of the importance of the work on the Rh factor by their co-operation. In accepting this ward, I do so humbly, fully realizing that our contribution represents only a small faction of the important work being done by scientists in America and abroad. I trust that our future work will justify this token of your confidence and the tradition laid down by the great path-finder Karl Landsteiner, whose many contributions I have attempted to describe to you from the viewpoint of a pupil, co-worker, friend and admirer.