



# Rh-Hr BLOOD TYPES

APPLICATIONS IN CLINICAL AND LEGAL MEDICINE  
AND ANTHROPOLOGY

Selected Articles in Immunohematology

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## **Rh-Hr BLOOD TYPES**

by the same author

**AN Rh-Hr SYLLABUS: The Types and Their Applications**



KARL LANDSTEINER  
Father of Immunohematology  
1868 - 1943

To  
Gertrude,  
Jane and Barbara

## ACKNOWLEDGMENTS

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American Journal of Clinical Pathology, American Journal of Diseases of Children, American Journal of Human Genetics, American Journal of Physical Anthropology, American Naturalist, Annals of Allergy, Annals of Eugenics, Annals of Internal Medicine, Bacteriological Reviews, Blood—The Journal of Hematology, British Medical Journal, Bulletin Dade County Medical Association, Bulletin of the World Health Organization, Current Medical Digest, Experimental Medicine and Surgery, Hereditas, Journal of the American Medical Association, Journal of Experimental Medicine, Journal of the History of Medicine and Allied Sciences, Journal of Immunology, Journal of Laboratory and Clinical Medicine, Amer. Journal of Obstetrics and Gynecology, Laboratory Digest, Lancet, Medical Clinics of North America, Pediatrics, Postgraduate Medicine, Proceedings of the Society of Experimental Biology and Medicine, Science, The Internist, Transactions of the New York Academy of Science, Transactions and Studies of the College of Physicians of Philadelphia.



## PREFACE

THE discovery of the rhesus factor in human blood by Landsteiner and Wiener in 1937 was soon followed by the demonstration of its role in hemolytic transfusion reactions by Wiener and Peters and its role in erythroblastosis by Levine, Burnham, Katzin and Vogel. As a result of this work a new field opened up, which has grown rapidly in complexity.

Because of the practical importance of this fascinating subject in clinical medicine (the subject also has important applications in general immunology, anthropology, and forensic medicine), a number of monographs on the Rh factor have appeared during the past few years, and there have been hundreds of articles and reviews written on this subject. While good reviews have the advantage of crystallizing accumulated knowledge, there is some demand for a volume containing the source materials upon which the conclusions are based. Therefore, it seemed worthwhile to collect in one volume the author's most representative and important contributions to this subject, thus giving an idea of how knowledge in this field developed.

Soon after the original Rh factor was discovered, it was found that this was part of a complex system in which there were several different Rh factors, as well as a number of reciprocally related Hr factors. Previous experience with the earlier developments regarding the heredity of the A-B-O groups led the present author to test the possibilities of whether the various Rh-Hr factors were inherited by separate pairs of genes or whether they represent factors within complex unit agglutinogens inherited by corresponding multiple allelic genes. It was possible to disprove the concept of independent or linked allelic gene pairs to account for the heredity of the Rh-Hr types, and therefore the theory of multiple alleles was adopted. A few years later, however, Fisher reintroduced the linked gene concept and elaborated it in collaboration with Race, even though this theory had previously been disproved and discarded. An unfortunate sequel to this development was the introduction of a different system of Rh-Hr nomenclature, and this has led to even greater confusion than was caused at one time by the Moss-Jansky numberings in the case of the A-B-O groups. The unsatisfactory nature of the C-D-E terminology of Fisher and Race is evident from the fact that as many as twenty different elaborate designations are in use to symbolize a single phenotype. Pertinent articles on this aspect of the subject are included in this volume, and as Amram Scheinfeld stated in a verse entitled "The Rh Blues,"

It's confusin' when transfusin'

Not to know the name of the blood you're usin'.

A minor disadvantage of a volume of collected reprints is the inevitable differences in terminology which occur as the subject develops. For example, the type now designated as rh' was at one time designated as Rh'. However, these small changes will cause no difficulty, especially to workers using the C-D-E notations, since even at the present time they use more than twenty different names for the same blood type. Other disadvantages are the danger of repetition, as well as the fact that ideas presented in earlier articles may no

longer be considered valid. These disadvantages have been avoided by the careful selection of articles, while the insertion of occasional explanatory editorial notes also helps to bring the subject matter up to date. Such notes are usually distinguished from the original article by the use of sanserif type.

Another interesting aspect of the subject is the discovery of new methods of detecting and titrating antibodies, notably through the conglutination and anti-globulin tests, and the test with enzyme-treated cells. Applications of these tests have led not only to the further clarification of the pathogenesis of erythroblastosis fetalis, but also to the discovery of immunologic mechanisms in acquired hemolytic anemia. The discovery of the pathogenesis of erythroblastosis fetalis led in turn, to the introduction of exchange transfusions for the treatment of the disease. The Rh-Hr types have found important applications in anthropology for classifying human races and in studies on biochemical evolution, as well as in medicolegal problems of disputed parentage. These and other important recent developments can be followed in the articles which are included in this volume.

To increase the usefulness of the volume, an author and subject index have been prepared. Thus, readers who wish to delve further into the subject can find references to additional important publications in the field which have appeared during the past decade. For a review of the earlier literature, the reader should consult the third (1943) edition of the author's book *Blood Groups and Transfusions*, to which the present volume acts as a supplement.

It seemed appropriate to begin with a short biography of Dr. Karl Landsteiner, father of the entire field of blood grouping, to whom the author is indebted for advice and guidance, particularly during his earlier years of research. A bibliography of the present author's publications is also included, which may prove useful for reference purposes. The paper numbers given in the table of contents refer to the listing in this bibliography.

The work presented in this volume represents a collaborative effort, which would not have been possible without the contributions of many associates, too numerous to list. The names of the more important collaborators are given as co-authors in the individual articles, but special mention is necessary of the work of Mrs. Eve B. Gordon who has collaborated with the author for the past fifteen years in the Serological Laboratory of the Office of the Chief Medical Examiner of New York City, as well as Dr. Irving B. Wexler who has participated in the work on exchange transfusion from the onset up to the present time. The author also wishes to express his appreciation to Misses Sara Barnett and Nancy Ercolono for their invaluable assistance over many years in the preparation of manuscript materials.

To Mr. Henry M. Stratton, the author wishes to express his appreciation for helpful suggestions regarding the preparation of the volume for publication.

ALEXANDER S. WIENER.

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## I. HISTORICAL BACKGROUND

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### 1. Karl Landsteiner

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## PART ONE

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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 feel sad, realizing that Dr. Karl Landsteiner, who played such an important rôle 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 worthwhile project on which to spend the vacation 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 4 A-B-O groups and the subgroups 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.

*\*Remarks made on the occasion of the Passano Award, Atlantic City, June 13, 1951.*

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 an heir, otherwise he was an impostor. 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 subgroup from the shape assumed 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 Member of the Rockefeller Institute for only 7 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 was no fundamental difference 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 theater, 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 thenceforth 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 realized 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 I, 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 smallpox but no other 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.