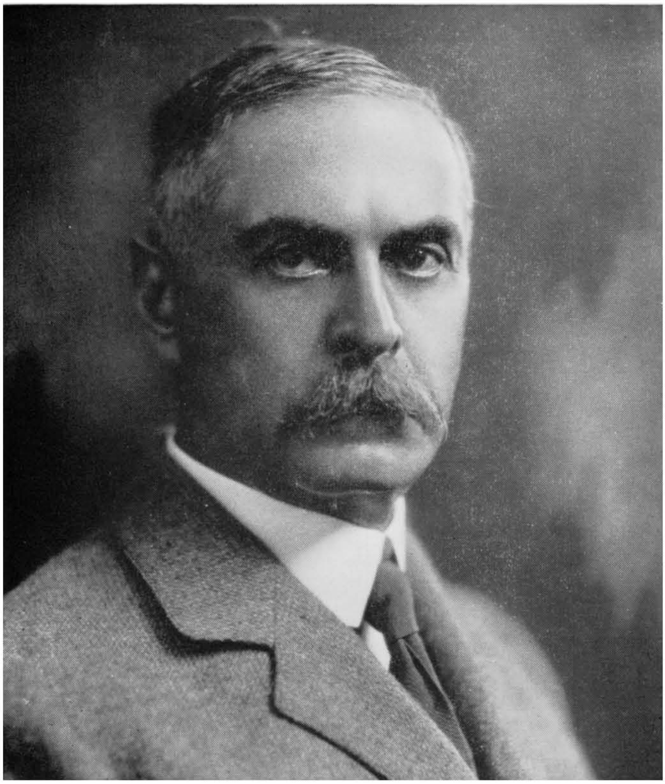
NATIONAL ACADEMY OF SCIENCES

KARL LANDSTEINER

1868—1943

A Biographical Memoir by
MICHAEL HEIDELBERGER

Biographical Memoir



K. Landsteiner

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June 14, 1868–June 26, 1943

BY MICHAEL HEIDELBERGER

THE TIME IS PAST when one man can know all of science. Karl Landsteiner was one of the last possessed of the tremendous intellect that could comprehend and, better still, use practically all of the scientific knowledge of his time. He had been classified as a pathologist, but he studied organic chemistry with Bamberger, Hantzsch, and Emil Fischer and used his mastery of it to lay the groundwork of the chemical basis of immunological specificity, and he later read Max Planck's *Quantum Theory* and assimilated that, too.

Karl Landsteiner was born in or near Vienna on June 14, 1868, eleven years after the marriage of his parents, Fanny Hess and Dr. (of laws) Leopold Landsteiner, a well-known Austrian journalist and editor. When Karl was six his father died and some years later mother and son left the Jewish faith and became Roman Catholics. Karl's schooling began at the age of five and in later years he was always well up in the top half of his class. Entering medical school in 1885, he soon began experimental work in chemistry under the guidance of Ernst Ludwig, who was said to have been one of the most inspiring teachers of his time. In 1891 Landsteiner was awarded the degree of "Doktor der gesamten Heilkunde," surely a comprehensive title for a young man who had not quite reached his twentythird birthday. In the same year he functioned in the clinic of the University Hospital in Vienna and began several years of advanced study and research in organic chemistry under Emil Fischer in Würzburg, Eugen von Bamberger in Munich, and Arthur Hantzsch and Roland Scholl in Zurich. Not only were the results published in papers with three of these outstanding men, but the knowledge of organic chemistry and the feeling for it gained in these years guided Landsteiner through his entire career, as we shall see.

Until his twenty-seventh year Landsteiner also served in the University's first surgical clinic. On January 1, 1896, he was appointed assistant in the Institute of Hygiene of Professor Max von Gruber, and there, in spite of crowded conditions, began Landsteiner's interest in, and fundamental contributions to, immunology and serology. Nearly two years later he transferred to the Pathological-Anatomical Institute of Professor Anton Weichselbaum and worked there productively until the end of 1907. During this period he performed countless autopsies and pathological examinations, managing nevertheless to carry on far-ranging research on a variety of topics. This was published in seventy-five papers, many of which were fundamental additions to medical knowledge.

As early as 1900 Landsteiner became convinced that the hemagglutination of one blood by another was a physiological phenomenon and not pathological, as had been thought. Following extensive tests on the red blood corpuscles and sera of patients, colleagues, and himself, he developed the concept of the three blood-groups A, B, and C (now known as O). Thus began a revolution in the care and treatment of patients that eventually robbed blood transfusions of their principal dangers and ultimately won for Landsteiner the Nobel Prize in Medicine.

Shortly after his first publications on the subject Landsteiner showed the value of blood grouping in the identification of bloodstains and in other medicolegal problems. However, there was a lag of years in the impetus to the increased use of transfusions of blood owing to the dangers and imperfect techniques which had previously made the procedure hazardous. It was not until 1907 that the first matching of bloods was carried out by Dr. Reuben Ottenberg of Mt. Sinai Hospital, New York, nor was the anticoagulant, sodium citrate, adopted until 1915. The principal problem today is to find enough donors for the rivers of human blood transfused. Studies on the chemistry of the blood-group substances have kept pace with the development of serological refinements and knowledge, and Landsteiner would certainly have rejoiced at the present state of the vast chapter of medicine and biochemistry for which he wrote the preface and laid down the fundamentals.

Other important discoveries were made by Landsteiner and his co-workers during his years in Weichselbaum's institute and these were mentioned in his "Habilitations" request for the "Venia legendi" or right to lecture. Independently of Jules Bordet, he showed that injection of foreign red blood cells into an animal gave rise to hemolysins and hemagglutinins. During this period, also, he discovered, with Donath, cold agglutinins, and so cleared up the mechanism of paroxysmal hemoglobinuria. He was also among the first, if not actually the first, to dissociate the products of the interaction of antigens and antibodies and so to prepare partially purified antibodies. He was the first to use the technique of dark-field microscopy for the identification and study of the spirochetes of syphilis, the first to show that the Bordet-Wassermann test for syphilis could be carried out efficiently with "antigens" extracted from organs of normal animals as well as from syphilitic tissues, and the first to transmit syphilis to monkeys.

On January 1, 1908, Landsteiner became chief of pathology at the Wilhelmina Hospital in Vienna. During the same year, he and E. Popper succeeded in transmitting poliomyelitis to monkeys and stated that the disease was apparently caused by a virus, thus laying the foundation for the further research that has resulted in the virtual elimination of this scourge. In 1911 Landsteiner received his first official recognition in an appointment to the Medical Faculty of the University of Vienna as Adjunct Professor without salary. During World War I he also served in War Hospital No. 1 and, in recognition of his services, was given the title of "Regierungsrat" in 1917. One year before, at the age of forty-eight, he married Helene Wlasto, who was twelve years his junior. A year later their only child, Ernst Karl, now a practicing physician in Providence, Rhode Island, was born.

At about this time, in spite of the difficulties caused by the war, Landsteiner began the studies which laid the foundation for the recognition of the chemical basis of immunological specificity. However, the lack of facilities for research, the civil disorders in Vienna, and the financial difficulties in making ends meet were so compelling that he transferred his activities to the Netherlands, where he was appointed "Prosektor" in a small Roman Catholic hospital at The Hague in 1919. The facilities and living conditions immediately after the war were better there than in Vienna, and while at The Hague Landsteiner began work on the immunology of hemoglobin and carried further the initial studies with azoproteins, to which further reference will be made. However, the uncertainties of his position made him receptive to an offer of a membership at the Rockefeller Institute in New York and this he decided to accept.

Karl Landsteiner and his wife and small son left their pleasant little house at the seaside in Scheveningen in the spring of 1923 and emigrated to New York, where Dr. Simon Flexner, Director of the then Rockefeller Institute for Medical Research, had invited Landsteiner to full membership, the highest rank in the Institute. Dr. Peyton Rous tells how, when met at the ship and asked what sort of living quarters he would need, Landsteiner said: "A little cottage by the sea with a rose garden, such as I had in Scheveningen . . . at about $50 a month." Needless to say, the flat ultimately selected represented a drastic compromise, and life in the big city was so different that Landsteiner often said that he wished he could lock his family in when he went out to work in the morning. However, readjustments were made and he became a citizen of the United States as soon as the law allowed.

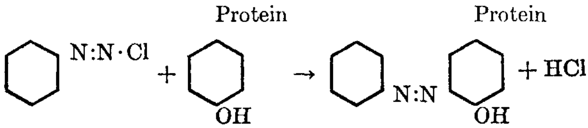
As a man of broad interests and knowledge, Landsteiner was fascinated by the work his fellow-members were doing at the Rockefeller Institute and immediately enlisted the help of some of them in several joint projects. The longest-lasting of these was the study of the heterogenetic hapten with P. A. Levene, head of the biochemical division, but even this was broken off eventually in a clash of temperaments. Landsteiner, mild-mannered and sensitive as he was, nevertheless became unmistakably the "Herr Geheimrat" and absolute director in his laboratory and always insisted on running crucial tests himself. Quite understandably, this did not go well with other "Geheimrats," and experiments begun with Alexis Carrel and with James B. Murphy were not carried to conclusion.

Before arriving in the United States, Landsteiner had published several papers on the heterogenetic antigen, clarifying the apparently contradictory data of earlier workers. He found that an immunologically specific portion could be separated from the complex, and that this material, which had the properties of a lipid, did not by itself stimulate the formation of antibodies. Landsteiner adopted the term "hapten" for such substances. The heterogenetic hapten could, however, be converted into a complete antigen by simple admixture with proteins such as pig serum, itself a mixture, and this was considered a "Schlepper," which "dragged" the hapten to the sites of formation of antibodies.

At the time Landsteiner arrived at the Institute I had developed a method in D. D. Van Slyke's laboratory in the Hospital of the Rockefeller Institute for the isolation of large quantities of crystalline horse oxyhemoglobin with an unimpaired capacity for release of, and combination with, oxygen. Landsteiner had previously studied the immunological properties of the hemoglobins of several species and he proposed that we inject horse oxyhemoglobin into rabbits and determine whether or not differences could be established between the oxyhemoglobins of different animal species. Conflicting answers to this question had been obtained by earlier workers. Landsteiner had just read Max Planck's book on the quantum theory and as a result suggested that, in addition to the serological tests, we run parallel physicochemical estimations of the solubility of each oxyhemoglobin in a saturated solution of the other. If there were no difference between the oxyhemoglobins, and if each were a single, pure substance, nothing more should dissolve. If, on the other hand, the oxyhemoglobins were chemically different, each should dissolve in a saturated solution of the other as in water alone. Tests along these lines showed clear differences between horse, dog, rat, and guinea pig oxyhemoglobins, while the oxyhemoglobins of the horse and donkey, two species which can be cross-bred, seemed identical or isomorphous.

Early in this century Pauly had shown that diazotized aromatic amines could be coupled to proteins and that colored products resulted in which the reaction had taken place mainly with the tyrosine and histidine residues. Obermayer and Pick used such azoproteins in attempts to alter the species specificity of proteins, but it was Landsteiner who realized the full implications of this reaction for immunology, seeing in it a means for modifying proteins in predictable ways by adding a great variety of simple substances which might influence the specificity of the native protein used.

The principal chemical reaction is:



Depending upon the relative proportions of diazotized aromatic amine and protein, varying degrees of modification could be induced. If, after injection of the yellow or orange azoderivative into rabbits, a precipitate formed when antigen was added to the animal's serum, it was necessary to determine whether this was due to reaction with the hapten or added portion of the molecule, or whether the precipitation was simply one due to the carrier; that is, a protein-antiprotein interaction. Landsteiner and his co-workers solved this difficulty by coupling the same hapten to another protein unrelated to that injected and found that the sera of some of the rabbits still precipitated with the new antigen, showing that they had actually formed anti-hapten. A further confirmation was that an excess of the aromatic amine or its salt inhibited the precipitation, just as a large excess of antigen usually shifts the precipitin reaction (antigen-antibody precipitation) into a region of inhibition. In these ways it was found possible to distinguish between an *ortho-*, *meta-*, or *para-*substituent on the aromatic ring, particularly when the substituent was an acid group such as -COOH, $-SO_3H$, or $-AsO_3H_2$. All of this furnished a clear demonstration of the chemical basis of immunological specificity.

Additional phases of this work followed the discovery by Avery and myself that polysaccharides were the determinants of type-specificity in pneumococci, and paralleled experiments of Avery and Goebel showing that D-glucose and D-galactose and even α- and β-glucosides could be distinguished immunologically by means of antibodies elicited in rabbits by antigens prepared by coupling the diazotized *para*-aminophenyl glycosides to proteins. Landsteiner and van der Scheer diazotized the *para*-aminobenzoyl derivatives of D-, L-, and DL-phenylaminoacetic acids and the amino-anilides of D-, L-, and meso-tartaric acids, coupled these to proteins, and showed that each stimulated the formation of distinctive antibodies. In this way immunological differences could clearly be shown between D- and L-isomers.

Landsteiner and van der Scheer also continued the former's earlier studies on the chemical and enzymatic degradation of proteins in an effort to solve the riddle of their specificities. With Landsteiner's characteristic thoroughness, they also began at the other end with peptides of known sequence. Glycylglycine, leucylglycine, glycylleucine, and leucylleucine were attached to proteins as haptens and it was found that the amino acid at the carboxy-terminal end exerted the stronger effect on specificity. With tri- and higher peptides of the same amino acids the results were less definite.

At about this time F. E. Kendall and I had developed methods for the quantitative measurement of many precipitating antibodies in units of weight. Landsteiner never made use of the method, contenting himself with reporting the results as +, ++, +++, etc. Whenever the writer visited Landsteiner's laboratory, Landsteiner would blushingly apologize for not using the new method, and it was necessary to assure him that for his purposes a mass of quantitative data would add little to the often sharp qualitative distinctions his results disclosed. Like Jacques Loeb, who laid the foundations of modern protein chemistry, Landsteiner confined himself to the simplest methods capable of leading to an unequivocal conclusion and rightly avoided more laborious analytical techniques when simple qualitative tests sufficed.

Another time, when Landsteiner was returning a visit, I reached for a copy of his book to get it autographed and discovered that it was missing. "Someone has stolen your book," I said. "That is the greatest compliment I ever received," said Landsteiner.

During the course of his epoch-making researches on the chemical basis of immunological specificity, Landsteiner carried forward two other major lines of work. One, with Philip Levine and A. S. Wiener, dealt with the chemistry and immunology of the blood-group factors. It added much to the knowledge of the human blood-factors M and N and resulted in the discovery of the Rh, or rhesus, factor, which many human beings share with rhesus monkeys and which was later shown to be responsible for the dreaded disease of infants, erythroblastosis fetalis. The blood-group factors of other primates were also studied and compared with those of the human species.

The second principal line of research, carried forward with John L. Jacobs and Merrill W. Chase, concerned itself with skin-sensitization and allergy. Simple chemical substances, such as chlorodinitrobenzene, which was known to produce industrial allergy, and picryl chloride, were shown to give rise to specific sensitization in guinea pigs. Experiments with other substances showed that only those capable of combining chemically with proteins could cause this effect, apparently reacting with one or more proteins of the skin or other tissues to form an antigen foreign to the animal. Similar principles were later shown to apply in man.

During his last years Landsteiner formed a warm friendship with Linus Pauling, and their discussions and arguments led Pauling not only to apply his great talents to immunology but also to contribute a chapter to the revised edition of Landsteiner's book, *The Specificity of Serological Reactions.*

Landsteiner became an Emeritus Member of the Rockefeller Institute in 1939, but continued working in his laboratory there with undiminished ardor. Although a sensitive musician and competent pianist, he gave up the piano in his later years. He was, moreover, greatly upset by the events of World War II and was uneasy over the noise, the high incidence of crime, and the hurried pace of life in a great city. Finally, his wife fell ill of cancer, and her illness weighed heavily upon him. In the last week of June 1943 he suffered a coronary obstruction and entered the hospital of the Rockefeller Institute for treatment. Therapy was unavailing, and there he died.

The honors conferred upon Landsteiner were numerous. He was a member or honorary or foreign member, as the case might be, of the National Academy of Sciences (to which he was elected in 1932), the American Philosophical Society, the American Society of Naturalists, the American Association of Immunologists, Académie des Sciences of France, the New York Academy of Medicine, the Pathological Society of Philadelphia (as well as that of Great Britain and Ireland), the Royal Society of London, the Royal Society of Medicine, the Medical Chirurgical Society of Edinburgh, la Société Belge de Biologie, the Royal Danish Academy of Sciences, die deutsche Akademie der Naturforscher, l'Accademia Nazionale dei Lincei, the Royal Swedish Academy of Sciences, and the Swedish Medical Society, and was a Chevalier of the Légion d'Honneur. Landsteiner was awarded the Paul Ehrlich Medal and the Nobel Prize in Medicine in 1930, the Dutch Red Cross medal in 1933, and the Cameron Prize in 1938, and was given the degree of Doctor of Science, *honoris causa,* by the universities of Cambridge and Chicago, and by Harvard University.

IN COMPILING this biographical memoir I have been greatly aided by the more comprehensive publication, *Karl Landsteiner,* by Dr. Paul Speiser (Vienna, Hollinek Bros., 1961), and by the thoughtful review of Landsteiner's career and personality prepared by Dr. Peyton Rous for the Obituary Notices of Fellows of the Royal Society, Vol. 5, March, 1947. I am most grateful to Dr. Rous and Dr. Speiser for permission to make use of their material.

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KEY TO ABBREVIATIONS

Ann. Inst. Pasteur = Annales de l'Institut Pasteur
Ann. Rev. Biochem. = Annual Review of Biochemistry
Arch. Derm. Syph. = Archiv fuer Dermatologie und Syphilis
Beitr. chem. Physiol. u. Path. = Beitraege zur chemischen Physiologie und Pathologie
Beitr. path. Anat. = Beitraege zur Pathologischen Anatomie und zur Allgemeinen Pathologie
Ber. deut. chem. Gesell. = Berichte der deutschen chemischen Gesellschaft
Biochem. Z. = Biochemische Zeitschrift
Centr. Bakteriol. Orig. = Centralblatt fuer Bakteriologie, Originale
Centr. Bakteriol. Ref. = Centralblatt fuer Bakteriologie, Referate
Compt. Rend. Acad. Sci. = Comptes Rendus de l'Académie des Sciences (Paris)
Compt. Rend. Soc. Biol. = Comptes Rendus des Séances de la Société de Biologie et de ses Filiales
Deut. Z. ges. gerichtl. Med. = Deutsche Zeitschrift fuer die gesamte gerichtliche Medizin
Jahresber. Ergebn. Immunitätsforsch. = Jahresbericht über die Ergebnisse der Immunitätsforschung
J. Am. Med. Assoc. = Journal of the American Medical Association
J. Exp. Med. = Journal of Experimental Medicine
J. Immunol. = Journal of Immunology
Klin. Wochschr. = Klinische Wochenschrift
Med. Klin. = Medizinische Klinik
Münch. med. Wochschr. = Münchener medizinische Wochenschrift
Oesterr. Sanitätswesen = Oesterreichische Sanitätswesen
Proc. Koninkl. Akad. Wetenschap. = Koninklijke Akademie van Wetenschappen te Amsterdam, Proceedings of the section of sciences
Proc. Soc. Exp. Biol. Med. = Proceedings of the Society for Experimental Biology and Medicine
Schweiz. med. Wochschr. = Schweizerische medizinische Wochenschrift
Sitzber. k. Akad. Wiss. = Sitzungsberichte der Königliche Akademie der Wissenschaften, Mathematisch-naturwissenschaftliche Klasse, Wien
Verhandl. 9. Kongr. deut. dermat. Gesell. = Verhandlungen des neunten Kongress der deutschen dermatologische Gesellschaft
Verslag Koninkl. Akad. Wetenschap. = Koninklijke Akademie van Wetenschappen te Amsterdam, Verslag van de Gewone Vergadering der Afdeling Natuurkunde
Wien. klin. Rundschau = Wiener klinische Rundschau
Wien. klin. Wochschr. = Wiener klinische Wochenschrift
Wien. med. Wochschr. = Wiener medizinische Wochenschrift

Zentr. allgem. Path. Path. Anat. = Zentralblatt fuer allgemeine Pathologie und Pathologische Anatomie
Zentr. Gynäkol. = Zentralblatt fuer Gynäkologie
Zentr. Physiol. = Zentralblatt fuer Physiologie
Z. Hyg. Infektionskrankh. = Zeitschrift fuer Hygiene und Infektionskrankheiten
Z. Immunitätsforsch. Orig. = Zeitschrift fuer Immunitätsforschung und Experimentelle Therapie Originale
Z. klin. Med. = Zeitschrift fuer klinische Medizin
Z. physiol. Chem. = Zeitschrift fuer physiologische Chemie

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