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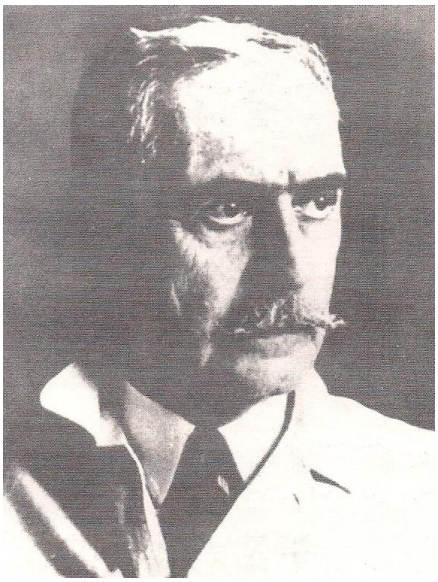
Author: Dr Frank Boulton, NBS Southampton

KARL LANDSTEINER AND THE DISCOVERY OF THE ABO BLOOD GROUPS



Karl Landsteiner

We commented last year on the 100th Anniversary of the preliminary notice by Landsteiner of his discovery of human blood groups. This year is the Centenary of the full announcement and naming of those groups. This seminal publication was cited as the main reason for recommending him for the Nobel Prize in 1930; it was also the first to recommend that blood groups be considered when blood is to be transfused.

Landsteiner - an only child - was born at Baden in June 1868. His father Leopold, was 50 and his mother Fanni, 31. Baden was a favourite summer resort for the Viennese middle classes but his birth had to be registered in Vienna as Baden had no Jewish Registry. Leopold, a journalist and writer, died 7 years later, so Karl's childhood was not easy. However, his family typified the degree of integration of the Jewish "professional classes" in Austria at that time - to be so tragically disrupted by Nazism. Apart from the registration of his birth (and circumcision), he bore his Jewishness lightly, being baptised into the Catholic Church in 1890.

At school he was above average but not outstanding - his best subjects being Mathematics and Science. He entered Vienna University in 1885 and served in the Army Medical Corps during 1889. He gained his Doctorate in February 1891, being deemed "excellent".

After qualifying he worked principally in the pathological sciences, including chemistry. In 1896 he began his lifelong work in immunology ("bacteriology and serology"). Two years later he was at the Vienna University Institute of Pathological Anatomy under Anton Weichselbaum, who had discovered the meningococcus. He helped Landsteiner to develop a disciplined approach to research. Landsteiner's work on blood groups was a small part of his output at that time - over eleven years he conducted 3639 autopsies.

From 1908 to 1920 Landsteiner took charge of the Department of Pathology at the Imperial Wilhelmina Hospital in Vienna. His mother died in April 1908, and in 1916 he married Helene Wlastos whose family by religion was Greek Orthodox. The disastrous effects of the First World War brought starvation to Vienna in 1919 and the new Republican Government of Austria could not afford to pay him; but he obtained work in The Hague, Holland, from 1919. However, it was a great relief when Simon Flexner invited him to join the Rockefeller Institute in New York in 1923. Even here, until after he gained the Nobel Prize, he still had only a small laboratory and could not continue his interest in poliomyelitis. Had he stayed in Vienna he would undoubtedly have suffered the same fate as his near contemporary, Sigmund Freud (who was 12 years older), and been expelled by the Nazis.

He continued in good health, working regularly - his last years as 'emeritus' at the Rockefeller - until his wife became ill with thyroid cancer. His anxiety brought on a fatal heart attack in June 1943. His wife died 6 months later. Their only son, Dr Ernst Landsteiner, became a surgeon in Providence, Rhode Island.

The Discovery of the ABO Blood Groups

Landsteiner made his discovery while studying immunised blood serum. His 1901 report is written in the formal academic mode then in vogue; the translation in the first issue of "Transfusion" gives a flavour of Landsteiner's style. Although describing in some detail the agglutination of normal human red cells by the serum of other healthy individuals, the report is surprisingly brief, and the data presented may - unwittingly - have been selected. This would be consistent with Landsteiner's diffidence about this work. He really regarded himself as an 'immunochemist'. When awarded the Nobel Prize, he delayed telling his family and later said that he would rather have got it for his work on the chemical nature of serological reactions.

There are three tables, and references to an unpublished fourth. The first describes reactions between the sera and cells of six "apparently healthy" men - Landsteiner and five associates including a Dr Sturli. The second describes similar reactions in six healthy puerperal women and repeats his demonstration ("law") that an individual's serum does not agglutinate his or her own red cells. Specific blood groups were not assigned, but we can see that of the six men, two - one being Landsteiner - were group O (which he called 'C'); two were A (or B); and two were B (or A). Among the women three were A (or B), two B (or A), and one O - the un-bracketed alternatives being slightly more likely as A is much commoner than B.

The third table describes reactions between sera of five of the puerperal women and red cells of six infants, three of whom were children of three of the women. The red cells of two babies were agglutinated by their mothers' serum. One of these mothers was O and her baby ?A; the other was ?A and her baby ?B (reactivity patterns indicate that the infant was not AB). The compatible mother/infant pair were both ?A. The serum of the sixth woman (who was ?B) was not featured although her baby's group O cells were. If Landsteiner's interest in peripartum samples signified a hunch about inherited characteristics, he would have been disappointed; but it was probably more to demonstrate that red cells of people free of disease, including new-borns, could be agglutinated. He missed the significance of the poor reactivity of neonatal serum, even though he noted it.

Tantalisingly, Landsteiner refers to more samples but dismisses them as *"presenting entirely identical regularities. The investigation of another ten more persons (in* 42 *combinations) gave similar results".* In all he tested 22 sera from healthy adults but, probably to clarify the variety of reactions, presented only 12 - in two sets of six. A

fuller publication would have indicated the ‘non-O’ frequencies better, and so which subjects were A and which B.

Transcript of a table from Landsteiner’s original article

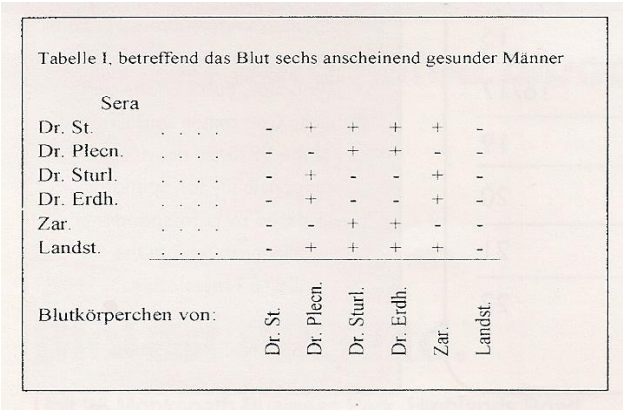


Tabelle I, betreffend das Blut sechs anscheinend gesunder Männer

Sera	Dr. St.	Dr. Plecn.	Dr. Sturl.	Dr. Erdh.	Zar.	Landst.
Dr. St.	-	+	+	+	+	-
Dr. Plecn.	-	-	+	+	-	-
Dr. Sturl.	-	+	-	-	+	-
Dr. Erdh.	-	+	-	-	+	-
Zar.	-	-	+	+	-	-
Landst.	-	+	+	+	+	-

Blutkörperchen von: Dr. St. / Dr. Plecn. / Dr. Sturl. / Dr. Erdh. / Zar. / Landst.

Landsteiner attributed the blood group determinant factor to the serum “agglutinin” (antibody). Therefore he labelled people with both types of agglutinin group ‘C’ because they had more reactivity than ‘A’ or ‘B’ people. He commented on other people’s findings of agglutinins in sera; Ehrlich showed what he called “isolysins” in animals, which Landsteiner felt were similar to his “isoagglutinins”. However, he was at a loss to explain the *“non-auto but iso-agglutination”* phenomenon (my italics).

He ends his paper with two points - the ability to recover agglutinating activity from blood dried on cotton cloth; and the last most pertinent (rather stiff) sentence - *“finally, it might be mentioned that the reported observations may assist in the explanation of various consequences of therapeutic blood transfusions*.”

Developments and later work

As only about 3% of the Viennese people would have been AB, it is not surprising that Landsteiner failed to find this group which was discovered by Sturli in 1902. In accord with Landsteiner’s concept, Sturli described this status as being of “no particular type” as there were no agglutinins in the serum. In an episode which touchingly reveals Landsteiner’s humanity he wrote to Sturli from Holland in 1921 almost pleading with him to make their association public so that he could share the glory of discovery of the “Fourth Blood Group (AB)”. He seemed sensitive to criticisms (from America) that he had discovered only three of them.

The fact that blood groups are determined by cell antigens was first recognised in 1910 by von Dungern and Hirschfeld in Heidelberg (who also found group A on chimpanzee erythrocytes). They called people with both agglutinins but no cell reactivity group ‘O’. This is more akin to zero, or perhaps “Ohne” (German for “without”). They also revealed that blood group inheritance was Mendelian in nature; Hirschfeld (also known as Hirzsfeld) went on to show that more people further East are group B.

The real hero who established the need for testing blood for compatibility was Reuben Ottenberg of New York who, when he began his work in 1908, did not realise that he was the first to apply Landsteiner’s discovery although he was aware of it. Because at that time blood for transfusion had to be obtained mostly from family members, Ottenberg observed that brothers and sisters often had the same blood group. After examining 54 families he concluded that they were inherited according to “Mendel’s

law". However Ottenberg still did not appreciate that blood group status was determined by antigens; this caused several inconsistencies, probably because some agglutinins reacted rather weakly in his test system.

In 1907 Janski, who was unaware of Lansteiner, described - in Hungarian - all four blood groups, naming them in order of frequency I, II, III and IV. In 1910 Moss of New York, who was aware of Landsteiner, labelled I and IV the other way around (see BBTS Newsletter 48). His main table shows three 'AB' people (among twenty), but confusion, prejudice in favour of the importance of the agglutinins (antibodies), and difficulty with classifying group 'C' caused him to devise his alternative nomenclature.

In all, Landsteiner published 346 papers - a considerable number for his time. In Vienna while researching syphilis he described the Donath-Landsteiner phenomenon (in which he claimed to have bested Ehrlich by demonstrating its occurrence *in vitro*). He also praised the work of Moreschi with his "proto-Coombs' test" (1908) and disagreed with Ehrlich's ideas about antibody formation being due to an overspill of "side chain receptors" - indicating that Landsteiner had a good insight into the nature of antigen-antibody reactions. When Ottenberg visited him in 1910 he was much more interested in his propagation of polio virus from monkey spinal cords than in blood groups. While in Holland he produced twelve papers (some in Dutch or English), began work on carcinogens in tar, the immunogenicity of animal haemoglobins and invented the word "hapten".

In New York he continued working on animal haemoglobins, on solublised bacterial antigens, and on the 'irregular' anti-A_1 agglutinins, before comparing 'serological factors related to human isoagglutinogens in the blood of lower monkeys'. This lead to his discovery in 1927 of blood groups P, and of M and N (apparently named from the word "immune", not because monkeys eat nuts). He formed an increasing conviction that - except for identical twins - individuals were serologically unique (the subject of his Nobel Award Lecture). Landsteiner's own "phenotype" was apparently "O, N, P-". But his major contribution to blood transfusion serology after ABO was his discovery of the Rh factor. With Philip Levine he injected monkey and human blood into rabbits or guinea pigs. After adsorbing out other antibodies, the processed sera revealed the Rh factor on human red cells as they agglutinated cells in 39 out of 45 human blood samples independently of their M, N, or P status. The same 39 samples were also agglutinated by the serum of a New York woman who had suffered several pregnancies affected by Haemolytic Disease of the Newborn. Although this reactivity is actually caused by varying concentrations of the genetically unrelated 'LW' antigens, this comparative analysis opened a new era in clinical transfusion serology.

Landsteiner was a remarkable scientist and discoverer. He was, however, very human and susceptible to foibles and mistakes - but this makes him all the more attractive. So many near-contemporary descriptions of Great Men (sic) are almost hagiographies; very few deserve such accolades - Landsteiner came closer than most.

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