The blood revolution initiated by the famous footnote of Karl Landsteiner's 1900 paper

Sachi Sri Kantha

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Abstract

A 1900 publication authored by Karl Landsteiner, at the age of 32 years, contained a footnote which stated that, "the serum of healthy human beings not only agglutinates animal red cells, but also often those of human origin, from other individuals". He followed up this statement in his 1901 paper, and concluded that, "My observations reveal characteristic differences between blood serum and red blood cells of various apparently healthy persons" and that "the reported observations may assist in the explanation of various consequences of therapeutical blood transfusions". These significant observations resulted in the discovery of A, B, O and AB blood groups and later led to successful blood transfusions in humans. The impact of this revolutionary finding by Landsteiner also changed a number of biomedical disciplines such as immunology, medical anthropology, forensic medicine, genetics and pathology.

Introduction

Ninety-five years have passed since the appearance of an unquestionably the most revolutionary footnote which adorned a biomedical publication. The author of this footnote was Karl Landsteiner (1868-1943), the Vienna-born medical doctor, who became the first American (albeit, naturalised American) to receive the Nobel Prize in medicine in 1930.

In this review, I present a review of the "blood revolution", fathered by Landsteiner, primarily based on his own descriptions.

Discovery of blood groups

Table 1 provides a chronological synopsis of Landsteiner's life, spent in three countries; his native Austria (1868-1919), the Netherlands (1919-1922) and the USA (1922-1943). In his only paper published in 1900 which dealt with natural antibodies, Landsteiner wrote in a footnote, "The serum of healthy human beings not only agglutinates animal red cells, but also often those of human origin.

<table>
<thead>
<tr>
<th>Year</th>
<th>Age</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 14, 1868</td>
<td>---</td>
<td>born to Leopold Landsteiner (a Viennese journalist) and Fanny Hess Landsteiner.</td>
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<tr>
<td>1874</td>
<td>6</td>
<td>lost his father and was subsequently brought up by his mother.</td>
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<tr>
<td>1891</td>
<td>23</td>
<td>graduated in medicine, from the University of Vienna; published his first paper on the influence of diet on the composition of blood ash.</td>
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<tr>
<td>1891-96</td>
<td>23-28</td>
<td>apprenticed at Hantzsch (Zurich), Emil Fischer (Wurzburg) and E. Bamberger (Munich).</td>
</tr>
<tr>
<td>1896</td>
<td>28</td>
<td>assistant to Max von Gruber at the Hygiene Institute in Vienna.</td>
</tr>
<tr>
<td>1898-1908</td>
<td>30-40</td>
<td>assistant at the department of pathological anatomy, University of Vienna, under A. Weichselbaum.</td>
</tr>
<tr>
<td>1908-19</td>
<td>40-51</td>
<td>'prosektor' at the Wilhelminasapital in Vienna; also, held the position of adjunct professor of pathological anatomy at the University of Vienna.</td>
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<tr>
<td>1919-22</td>
<td>51-54</td>
<td>prosektor at a small Roman Catholic hospital in Hague, Netherlands.</td>
</tr>
<tr>
<td>1922-43</td>
<td>54-75</td>
<td>researcher at the Rockefeller Institute for Medical Research in New York.</td>
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<tr>
<td>1930</td>
<td>62</td>
<td>awarded the Nobel Prize in medicine for his pioneering discovery of blood groups.</td>
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<tr>
<td>June 26, 1943</td>
<td>75</td>
<td>suffered a heart attack, while working in his laboratory and died.</td>
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1 Research Scientist, Japan Institute for Control of Aging. 723-1 Haruoka, Fukuroi City, Shizuoka 437-01, Japan.
gin, from other individuals. It remains to be seen whether this appearance is related to inborn differences between individuals or it is the result of some damage of a bacterial kind”(1,2).

That was quite a significant observation, and a prophetic inference. In the very next year, Landsteiner published a short, definitive paper entitled, “On agglutination of normal human blood”(3), describing his pioneering effort on the identification of there blood groups. He began his classic paper as follows:

“Sometime ago I observed and reported that serum of normal humans frequently agglutinates red blood cells of other healthy individuals. At that time I was under the impression that this ability of the serum to agglutinate foreign red cells was especially pronounced in some diseases and I believed that this agglutinating ability was related to the strong lytic ability of pathologic sera of normal red cells which was observed by Maraglino many years ago”(3).

Following a few comments on the differences between his observations and that of Maraglino’s (reported in 1892), Landsteiner wrote, “My observations reveal characteristic differences between blood serum and red blood cells of various apparently healthy persons”. After presenting the agglutination results in three simple tables, which represented the experiments conducted in the blood of six men, six puerperal women and six placentae (cord blood), Landsteiner concluded the report stating that, “the reported observations may assist in the explanation of various consequences of therapeutical blood transfusions”.

Landsteiner used his blood also in the described agglutination experiments, and it could be inferred from the table of his 1901 paper, that he belonged to the O blood group (4). His junior colleague Alexander Wiener had noted in his reminiscences that, the group O (read as the alphabetical letter, “Oh”) was “originally intended as a zero, meaning neither A nor B” (4). The fourth major blood group AB was first reported by de Castello and Sturli in 1902 (5). Landsteiner was the mentor to Sturli. In 1903, Landsteiner and Richter published a paper suggesting the practical application of grouping dried human blood stains for use in forensic medicine (6).

Contributions to microbiology

For nearly two decades from 1903 to 1922, Landsteiner shifted gears and focussed his attention on microbiology. His discoveries during this period include the following (7).

1. elucidation of the pathogenesis of paroxysmal hemoglobinuria (with Donath)
2. introduction of dark field microscopy for diagnosis of syphilis
3. development of complement fixation test for syphilis
4. identifying the viral origin of poliomyelitis
5. cultivation of Rickettsia in tissue cultures (with Nigg)
6. pathogenesis of contact dermatitis
7. theory of hypersensitiveness to drugs
8. the concept of haptons and laying the foundations of immunochemistry
9. clarifying the specificity of plant agglutinins

Landsteiner returned to the studies on blood groups, after becoming a member of the Rockefeller Institute at New York in 1922. He was awarded the Nobel Prize for physiology or medicine in 1930, “in recognition of his discovery of human blood groups”.

Nobel lecture and research during post-Nobel award period

Since three decades had lapsed from the publication of his initial report and the Nobel Prize recognition, in his Nobel award lecture, delivered on December 11, 1930, Landsteiner presented in detail, the practical significance of his vital discovery. He observed that,

“there exist characteristic differences [in the relative frequency of the blood groups] in different races... the behaviour of the blood groups, in conjunction with other anthropological features, allows conclusions to be drawn regarding the relationship and origin of human races and is of some importance to anthropological research”(8).

Continuing further, Landsteiner stated that, “more often blood group reactions have been used in forensic medicine for the purpose of establishing paternity... In a survey which appeared last year [1929], Schiff reported that, of 5000 forensic investigations, paternity was excluded in more than 8% of the cases, although the theoretical proportion of cases in which exclusion should be possible is 15%. In favour of the method, it can be mentioned that it has also been instrumental in inducing some fathers to recognise their illegitimate child”(8).

“More important to practical medicine than the subject with which we have just been dealing”, stressed Landsteiner, “is the use of the blood group reaction in transfusion... The first blood transfusion in which the agglutinin reaction was taken into account was carried out by
Ottenberg, but it was only during the emergencies of the Great War [World War I] that the method of transfusion with serological selection of donor was widely adopted - a method which has since remained the normal practice...."

After providing statistics on blood transfusions carried out in New York and in Kiel, “without one fatal incident”, Landsteiner concluded his Nobel address in an optimistic note; “All in all, the results of blood transfusion are highly satisfactory. In addition we have reason to hope that thorough study of cases with undesirable after effects will help us to confirm suspected causes and perhaps reveal unknown cases, and thus finally virtually eliminate slight risks which transfusion still involves”(8).

Considering that the first trials on transfusion of animal blood to humans were conducted in 1667, and that the first transfusion with human blood was carried out during the first half of the 19th century, it becomes apparent that the transfusion experiments became successful only after the discovery of different blood groups by Landsteiner. Farr (9) has presented a historical survey of the confusions which existed among clinicians related to blood grouping and transfusion practice during the first four decades of this century.

Landsteiner was 62 years old when he received the Nobel Prize. His research endeavours continued for another 13 years. The first edition of his definitive work, Spezifitaet der Serologischen Reaktionen (The Specificity of Serological Reaction) was published 1936. At the age of 72, Landsteiner in association with Wiener reported another landmark discovery; “An agglutinable factor in human blood recognized by immune sera for Rhesus blood” (10). This is the now well known ‘Rh factor’, the absence of which in the mother could be harmful to her foetus. Till his death, after reaching 75 years in June 1943, Landsteiner continued to publish papers on the Rh factor, with titles such as, ‘Distribution of the Rh factor in American Indians’, “Tests for the Rh factor with guinea pig immune sera” and “Heredity of variants of the Rh type”.

Consummate clinician and researcher

In the words of Joseph Goldstein, the 1985 co-Nobelist in medicine, “His (Landsteiner’s) medical training was in pathology, and he personally performed 3639 autopsies during the first 10 years of his career—one autopsy a day, seven days per week for 10 years. What’s amazing to believe is that his major scientific discovery came in the midst of this enormous clinical load. Landsteiner’s curiosity was aroused by the clinical problem of massive hemolysis and generalised tissue destruction that occurred in patients who died after blood transfusions or injections of foreign protein. He wondered whether the serum of sick patients might act on the cells of healthy individuals. This stimulated him to investigate whether red cells agglutination and hemolysis could be detected in a test tube. Fortunately, Landsteiner had a strong background in organic chemistry. He applied his chemical knowledge to the clinical problem of transfusion reactions and the result was the discovery of A, B and O blood groups and the theory of chemical immunity”(11).

Conclusion

The blood revolution initiated by the famous footnote of Landsteiner’s 1900 paper changed the face of many biomedical disciplines, such as immunochemistry, medical anthropology, forensic medicine, genetics and pathology. From a practical perspective, successful blood transfusions in humans became routine, and gave life and hope to millions.

References

3. Landsteiner K. Ueberagglutinationerscheinungen normalen menschlichen blutes. Wiener Klinische Woehenschrift, 1901; 1: 5-8 (an English translation is provided by, Kappus AL, Transfusion, 1961; 1: 5-8).