HISTORICAL PROFILE

A Centennial Review; the 1890 Tetanus Antitoxin Paper of von Behring and Kitasato and the Related Developments

Sachi Sri Kantha

Department of Physiology and Biochemistry, Medical College of Pennsylvania, Philadelphia, PA, USA

(Received for publication on August 13, 1990)

Abstract. The significance of the 1890 tetanus antitoxin paper by von Behring and Kitasato in the development of a new discipline, immunology, is reviewed. The possible reasons why Kitasato lost the first Nobel Prize for medicine to von Behring are presented. These are as follows: (1) The Nobel selection committee literally interpreted Alfred Nobel's will to award the prize to "the person who has made the most important discovery." (2) In the late 19th century, diphtheria was a serious contagious disease which claimed many thousands of lives in the Europe and America; and von Behring's solely authored paper on diphtheria antitoxin clinched the award for him. (3) The merit of tetanus antitoxin to humans, which was the focal point of the 1890 paper on tetanus antitoxin jointly authored by von Behring and Kitasato, was not recognized at the time of the award in 1901; it became apparent only during the First World War. (Keio J Med 40 (1): 35–39, March 1991)

Key words: Shibasaburo Kitasato, Emil von Behring, Nobel Prize for medicine, history of immunology

Introduction

December 4th 1890 marks the centenary of the publication of the classic paper entitled "On the mechanism of immunity to diphtheria and tetanus in animals," by von Behring and Kitasato¹ which signalled the birth of a new discipline called serology (immunology). This paper was published in the journal *Deutsche Medizinische Wochenschrift*. The term 'antitoxin' was first introduced in this paper, in its variant as 'antitoxisch'.²

As I have reported previously,³ even in Japan when Tonegawa was awarded the 1987 Nobel Prize for medicine for his contributions to immunology, adequate credit was not given to the contribution of Kitasato, who initiated this new discipline. The editors of the *Scandinavian Journal of Immunology*⁴ consider that this indifference is due to the "lack of knowledge of the history of immunology among the contemporary scientists." This is somewhat revealed by the way Tonegawa began his 1987 Nobel lecture.⁵ He referred to a letter his mentor Renato Dulbecco (the 1975 Nobel in Medicine) sent him in 1970 suggesting a possibility that he might work in the Basel Institute of Immunology, Switzerland, under Niels K. Jerne (the 1984 Nobel in Medicine). He did not acknowledge the achievements of

the past scientists of an earlier generation (especially Kitasato) who provided a stepping stone for him to initiate his research.

Though Tonegawa failed to mention anything about the 1890 paper of von Behring and Kitasato, his mentor Jerne in his 1984 Nobel lecture did address the debt of immunologists to the trend-setting work of these two pioneers. Jerne told the audience, "Let me first recall some of the essential elements of the immune system, with which I shall be concerned. In 1890, von Behring and Kitasato were the first to discover antibody molecules in the blood serum of immunized animals, and to demonstrate that these antibodies could neutralize diphtheria toxin and tetanus toxin. They also demonstrated the specificity of antibodies; tetanus antitoxin cannot neutralize diphtheria toxin and *vice versa*."⁶

In this paper, I review the significant elements of the 1890 paper by von Behring and Kitasato and the possible reasons why Kitasato lost the first Nobel Prize for medicine to von Behring.

The Two Trend-setting 1890 Papers

The gist of the experimental procedure adopted by von Behring and Kitasato in their 1890 paper relates to

(a) immunizing rabbits against a culture containing virulent tetanus bacilli; (b) collecting blood from the carotid artery of rabbits; (c) injecting 0.2–0.5 ml of blood fluid (before coagulation) into the abdominal cavity of mice; and (d) inoculating the mice with virulent tetanus bacilli, and after 24 hours observing the effect of immunity. von Behring and Kitasato made four inferences in their landmark paper.⁷

1) “The blood of rabbits immune to tetanus has the ability to neutralize or destroy the tetanus toxin.”

2) “This property exists also in extravascular blood and in cell-free serum.”

3) “This property is so stable that it remains effective even in the body of other animals, so that it is possible, through blood or serum transformations, to achieve an outstanding therapeutic effect.”

4) “The property which destroys tetanus toxin does not exist in the blood of animals which are not immune to tetanus, and when one incorporates tetanus toxin into non-immune animals, the toxin can still be demonstrated in the blood and other body fluids of the animal, even after its death.”

Their paper concluded with a paraphrase from Goethe's Faust “The results of our experiments remind us forcibly of these words: ‘*Blut ist ein ganz besonderer Saft*’ (Blood is a very unusual fluid).”

A week later, von Behring alone published another paper entitled, “Studies on the mechanism of immunity to diphtheria in animals” in the *Deutsche Medizinische*

Wochenschrift.⁸ He introduced this paper with the comment,

“In No. 49 of this journal, Kitasato and I reported on experiments which show that the immunity to tetanus of experimental animals resides in the ability of the blood to render harmless the toxic products of the tetanus bacillus. The same mechanism was advanced in that paper for diphtheria immunity, without actually reporting experiments which supported this idea. It is the purpose of this paper to present this data.”

He also had commented that since mice and rats are naturally immune to diphtheria, he used guinea pigs to test the mechanism for immunity to diphtheria. It has been pointed out by Lindenmann² that, von Behring did not use the words ‘antitoxic’ or ‘antitoxin’ in this second paper.

A Survey of Contemporary Citations to the 1890 Tetanus Antitoxin Paper

Table 1 provides a random survey of the immunology books in which citations to the 1890 discovery of the tetanus antitoxin has appeared. Among the 12 English language text books on immunology, although six make proper citation to the contributions of von Behring and Kitasato,^{10–13,15,19} the other six attributed credit only to von Behring and omitted the name of Kitasato.^{9,14,16–18,20} However, three books surveyed^{7,21,22} on the history of immunology provided adequate credit to

Table 1 A survey of Contemporary Citations to the 1890 Tetanus Antitoxin Paper in Immunology Books.

Author and Year of Publication	Citation to 1890 Discovery		Reference
	von Behring and Kitasato	von Behring Only	
<i>Textbooks</i>			
Macfarlane Burnet (1969)		+	9
Humphrey and White (1971)	+		10
Carpenter (1975)	+		11
Benacerraf and Unanue (1979)	+		12
Klein (1982)	+		13
Clark (1983)		+	14
Grabar (1984)	+		15
Myrvik and Weiser (1984)		+	16
Playfair (1984)		+	17
Roitt (1984)		+	18
Silverstein (1984)	+		19
Barrett (1988)		+	20
<i>History books</i>			
Parish (1968)	+		21
Bibel (1988)	+		7
Silverstein (1989)	+		22

Note: Only those books in the English language which cite the 1890 discovery are specifically mentioned by in this survey. Many immunology textbooks do not provide a historical synopsis of the development of immunology as a discipline.

Kitasato in their descriptions of the discovery of tetanus antitoxin.

Of the 12 text books surveyed, two were authored by Nobelists in Medicine; Macfarlane Burnet⁹ and Baruj Benacerraf.¹² While Benacerraf has provided proper citation to the 1890 discovery in his text book, Macfarlane Burnet (considered one of the leading figures of 20th century immunology) has not mentioned Kitasato's name in his citation of the 1890 discovery. One could attribute this indifference on the part of some immunologists in omitting Kitasato's name to his omission from the 1901 Nobel Prize for medicine, which was awarded only to von Behring.

1901 Nobel Prize to von Behring

Von Behring was awarded the first Nobel Prize for medicine in 1901, "for his work on serum therapy, *especially its application against diphtheria*, by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and death."²³

The clues for why research on diphtheria (and not tetanus) was awarded the first Nobel prize could be discerned in the presentation speech made by Mörner in presenting the 1901 prize to von Behring. He told the assembled audience that,

"As far back in time as the knowledge of human illnesses extends, diphtheria and its modification croup have been a scourge of the human race. . . . For many decades now, it has raged among the various nations of the civilized world. . . .

"Up until now, serum therapy has had particularly splendid triumphs in the case of diphtheria, but its significance is not limited to this disease. The field opened up for research by the development of serum therapy has therefore — for the present — no discernible limits. . . . The pioneer in this new area of medical research, Professor Emil von Behring, has been chosen by the Medical Faculty of the Karolinska Institute as the recipient of this year's Nobel Prize for medicine."²⁴

Von Behring presented his Nobel lecture entitled, "Serum therapy; the Science and Art of Healing."²⁵ Some noticeable features of his Nobel lecture were:

- 1) His acknowledgment of the debt to pioneering work by Löffler and Roux on diphtheria bacillus.
- 2) Absence of any mention of his research on tetanus, conducted in collaboration with Kitasato (Kitasato's name does not appear even once in the lecture).
- 3) His description of his research on tuberculosis in cattle, in the second half of his address.

Von Behring concluded his lecture by stating, "I procured for myself living space and grazing ground for a large number of cattle and I am hoping to use the very generous monetary award which has come to me through

the Nobel Foundation to show the possibility and practicability of fighting tuberculosis in cattle along the lines of Pasteur's protective inoculation to a greater extent than has been done. It would give me much pleasure if any of you would care to inspect my Marburg work and installations and see, at the same time, how I am doing what I can in accordance with the intention of the noble founder himself, Alfred Nobel, to promote the common good."²⁵

It seems puzzling now why von Behring (a) did not include in his lecture, any reference to his collaborative research with Kitasato on the discovery of tetanus antitoxin published in 1890; and (b) devoted almost half of the lecture to his research on cattle tuberculosis, probably initiated in the late 1890s. One possible reason is that, since he was chosen as the first recipient of the prize among a field which included his mentor (and later an adversary) Robert Koch whose speciality was in tuberculosis therapy, von Behring wanted to impress his audience about his own research on tuberculosis in cattle.

Was Kitasato Nominated to the Nobel Prize?

The Daily Yomiuri of March 28, 1988 published a front page news report stating that it has obtained a document released by the Nobel Foundation in 1988, "which analyzed the deliberations of the minutes of the proceedings for recommendations for awards in physiology or medicine from 1901 to 1920."²⁶ According to this report, there were 46 nominees for the first Nobel Prize for medicine in 1901, which included the names of P Ehrlich, C Golgi, S Kitasato, R Koch, E Metchnikoff and S Ramon y Cajal. This list was pruned to 15 names after deliberations and Kitasato's name still remained. However at a later stage, "Emil A von Behring who had not even appeared on previous lists of hopefuls, was recommended for his pioneer work in serotherapy for diphtheria. Behring was nominated officially and became the first honorable winner of the Nobel Prize in physiology and medicine, a conclusion concerned parties had hardly expected."²⁶

This news report also mentioned that for the next 20 years, Kitasato's name never appeared in the list of nominees.

Possible Reasons for Kitasato's Non-recognition in the Nobel Awards

Though many non-scientific reasons could be attributed to why Kitasato did not receive equal recognition with von Behring in the 1901 Nobel award, three plausible reasons which could be suggested are as follows:

The Nobel selection committee's 'literal interpretation' of Alfred Nobel's will 1918.

The Nobel will, signed on November 27th 1895, stated that five prizes (of which one is to physiology and medicine) were to be awarded to "persons who, during the preceding year, shall have rendered the greatest services to mankind." As to the prize in physiology and medicine, the specific reference was to "the person who has made the most important discovery in the field of physiology and medicine."²⁷

It is not inappropriate to suggest that while the selection committee for the 1901 Medicine prize could not carry out Nobel's stipulation that the awardee be the one "who, during the preceding year shall have rendered the greatest services to mankind" (since von Behring's discovery was made ten years earlier), it managed to literally satisfy Nobel's other recommendation that "the person who has made the most important discovery" be recognized. Of the three science prizes, the Chemistry and Medicine prizes continued for the first two decades to be awarded to a single nominee.

High prevalence of diphtheria as a serious contagious disease

Diphtheria, though infrequent in the tropics, was an important cause of death among children in Europe and America in the late 19th century. According to von Behring's estimate, in Germany alone, the antitoxin treatment produced a reduction of 75% in the mortality from diphtheria, saving almost 45,000 human lives.²⁸ This was the type of example, the Nobel selection committee would have felt suited the ideals of Nobel's stipulation of "rendering the greatest services to mankind."

The recognition of the merit of tetanus antitoxin to humans was not evident at the time of the award

Compared to the mortality caused by diphtheria, tetanus (though a deadly killer) did not produce such a visible image as a public health problem around 1900. So, when deliberations for the selection of the 1901 prize were made, Kitasato's research contribution on tetanus was yet to be proven as a benefit to the mankind. There is no doubt that Kitasato's establishment of the tetanus antitoxin theory^{29–32} did influence von Behring's development of diphtheria antitoxin therapy. However the Nobel selection committee for the 1901 prize clearly seems to have ignored von Behring's intellectual debt to Kitasato. It is also ironic that the First World War (1914–18) confirmed the efficacy of tetanus antitoxin in preventing tetanus among several hundred thousands of wounded soldiers.³³ The World War also resulted in the suspension of Nobel awards for medicine from 1915 to

Conclusion

Though Kitasato lived till 1931 (and hence was eligible for Nobel recognition for almost another decade after the resumption of the Nobel awards in 1919), his 1890 contribution failed to receive Nobel merit. Between 1919 and 1930, two more unshared prizes were awarded to research on serology and immunology. Jules Bordet, who had followed Kitasato in the field of serology, was the recipient of the 1919 Nobel Prize in Medicine "for his discoveries in regard to immunity." The 1930 Nobel Prize in Medicine honored another pioneer of immunology, Karl Landsteiner, "for his discovery of the human blood groups" in 1900.

The reason that Kitasato's 1890 discovery was becoming "too old for recognition" in the 1920s is difficult to accept, since Landsteiner was recognized by the Nobel committee three decades after the appearance of his original publication. I agree with historian Bartholomew's recent comments that the exclusion of Kitasato from the 1901 Nobel Prize in Medicine has not yet been satisfactorily explained.³⁴

References

1. Von Behring E, Kitasato S: Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren. Dtsch Med Wochenschr 16: 1113–1114, 1890 (in German)
2. Lindenmann J: Origin of the terms 'antibody' and 'antigen'. Scand J Immunol 19: 281–285, 1984
3. Sri Kantha S: A review of Nobel Prizes in medicine or physiology, 1901–87. Keio J Med 38: 1–12, 1989
4. Harboe M, Møller E, Natvig JB, Wigzell H: The Nobel lectures in immunology. Scand J Immunol 30: 1–2, 1989
5. Tonegawa S: Somatic generation of immune diversity (Nobel lecture). Angew Chem Int Ed Engl 27: 1028–1039, 1988
6. Jerne NK: The generative grammar of the immune system (Nobel lecture). Angew Chem Int Ed Engl 24: 810–826, 1985
7. Bibel DJ: Milestones in Immunology: A Historical Exploration, Science Tech Publishers, Madison, WI, 1988, 12–15
8. Von Behring E: Untersuchungen über das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren. Dtsch Med Wochenschr 16: 1145–1148, 1890 (in German)
9. Macfarlane-Burnet F: Cellular Immunology, Melbourne University Press, Victoria, 1969, 5
10. Humphrey JH, White RG: Immunology for Students of Medicine, 3rd Ed, Blackwell Scientific Publications, Oxford, 1971, 5
11. Carpenter PL: Immunology and Serology, 3rd Ed, WB Saunders, Philadelphia, 1975, 2
12. Benacerraf B, Unanue ER: Textbook of Immunology, Williams & Wilkins, Baltimore, MD, 1979, 2
13. Klein J: Immunology; the Science of Self-Nonself Discrimination, John Wiley and Sons, New York, 1982, 32
14. Clark WR: The Experimental Foundations of Modern Immunology, 2nd Ed, John Wiley & Sons, New York, 1983, 3
15. Grabar P: The historical background of immunology. In: Basic and Clinical Immunology, 5th Ed, Stites DP, Stobo JD, Dudenberg HH, Wells JV, eds, Lange Medical Publications, Los Altos, 1984, 2, 10

16. Myrvik QN, Weiser RS: *Fundamentals of Immunology*, 2nd Ed, Lea & Fibiger, Philadelphia, 1984, 5
17. Playfair JHL: *Immunology at a Glance*, 4th Ed, Blackwell Scientific Publications, Oxford, 1987, 38
18. Roit IM: *Essential Immunology*, 5th Ed, Blackwell Scientific Publications, Oxford, 1984, 3
19. Silverstein AM: The history of immunology In: *Fundamental Immunology*, Paul WE, ed, Raven Press, New York, 1984, 27, 36
20. Barrett JT: *Textbook of Immunology*, 5th Ed, CV Mosby, St Louis, 1988, 11
21. Parish HJ: Victory with Vaccines; the Story of Immunization, E and S Livingstone Ltd, Edinburgh, 1968, 46–47, 54
22. Silverstein AM: *A History of Immunology*, Academic Press, San Diego, 1989
23. Schlessinger BS, Schlessinger JH: *The Who's Who of Nobel Prize Winners*, Oryx Press, Phoenix, AZ, 1986, 79
24. Mörner KAH: Presentation speech for the Nobel Prize in physiology or medicine, 1901. *Scand J Immunol* 30: 4–5, 1989
25. Von Behring E: Serum therapy in the science and art of healing (Nobel lecture, 12 Dec. 1901). *Scand J Immunol* 30: 6–11, 1989
26. 4 Japanese Savants in 1900s Narrowly Missed Nobel Prize, *The Daily Yomiuri*, Mar 28, 1988, 1
27. Evlanoff M, Fluor M: *Alfred Nobel: The Loneliest Millionaire*, Ward Ritchie Press, Los Angeles, 1969, 193
28. MacNalty AS: Emil von Behring. *Brit Med J* 1: 668–670, 1954
29. Kitasato S: Ueber dem Tetanusbacillus. *Zeitschr Hyg Infekt* 7: 225–234, 1889 (in German)
30. Kitasato S: Ueber den Tetanuserreger. *Dtsch Med Wochenschr* 15: 635–636, 1889 (in German)
31. Kitasato S: Experimentelle untersuchungen über das Tetanus gift. *Zeitschr Hyg Bd* 10: 267–305, 1891 (in German)
32. Kitasato S: Heilversuche an tetanuskranken thieren. *Zeitschr Hyg Bd* 12: 256–260, 1892
33. Browning CH: Emil Behring and Paul Ehrlich; their contributions to science. *Nature* 175: 570–575, 1955
34. Bartholomew JR: *The Formation of Science in Japan; Building a Research Tradition*, Yale University Press, New Haven, 1989, 5