Medicine in Stamps

Emil von Behring (1854–1917): Medicine's first Nobel laureate

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"Blood is quite a peculiar juice," intimates Mephistopheles in the 1808 Goethe classic *Faust*. Emil Behring—the German honorific "von" was bestowed on him later—echoed these words in his seminal 1890 manuscript on "serum therapy." In 1901, he received the first Nobel Prize in Medicine for this peculiarity and its application to the treatment of diphtheria. His lifesaving discovery of "serum therapy," or passive humoral immunity, canonised him as a father of modern immunology.

Emil Behring was born on March 15, 1854 in Hansdorf, Prussia to a family of modest means. Emil was one of thirteen children, and his family lacked the financial resources to continue paying for his education. Fortunately, his teachers intervened, citing his scientific aptitude, and provided him with a stipend and free board. He went on to medical school at The Friedrich Wilhelm Institute in Berlin, which was established to train Prussian military surgeons. Sent to Poland after internship, Behring found time to pursue research on the antitoxic effects of iodoform, and his talents soon won him a transfer to Berlin, where he joined Robert Koch's staff at the Institute of Hygiene, and later, at the Institute for Infectious Diseases.

AGE OF DISCOVERY The later years of the 19th century were remarkable times in the fields of immunology and microbiology. Louis Pasteur demonstrated that microbes caused illnesses, and developed early vaccines for anthrax and rabies. Robert Koch discovered the microbial aetiology of anthrax, tuberculosis and cholera. Edwin Klebs and Fredrick Loeffler discovered *Corynebacterium diphtheriae*, and Shibasaburo Kitasato isolated *Clostridium tetani*. Yet, there remained a disconnect between the identification of these microorganisms and the cure for the diseases they caused. Although Pasteur had demonstrated that vaccination with attenuated pathogenic bacteria was protective against future illness, the treatments for active disease remained elusive. It was Behring, in conjunction with Kitasato, who first bridged that gap.

A DEADLY SCOURGE Diptheria had been a scourge of humanity since ancient times. The first description of diphtheria in the ancient medical literature appeared in the second century AD. Medical writings in Greek and Latin described the classic symptoms: acute inflammation of the throat and larynx, stridor and airway obstruction, and in many cases, death. It is now known whether the exotoxin produced by *Corynebacterium diptheriae* also produces myocardial dysfunction and neuropathy. Children were particularly susceptible to the illness. Before Behring's discovery, 50,000 children in the German empire died of dipththeria each year. There was no known cure or palliative therapy other than tracheotomy performed as a method of last resort to prevent strangulation from the occluded airway.

Two manuscripts published in December of 1890 described groundbreaking research on a cure for diphtheria. In the first of these, "On the realization of immunity in diphtheria and tetanus in animals", Behring and Kitasato described how the inoculation of animals with sterilised cultures of diphtheria or tetanus caused them to produce antitoxins in the blood. "The immunity of rabbits and mice which have been immunized against tetanus," they wrote, "rests on the capability of cell-free blood serum to render harmless the toxic substances which the tetanus bacilli produce." The second paper described how the injection of antitoxins produced in one animal could immunise and cure another. The prospect of cure was no longer to be denied. His wife, Else Spinola

was a beneficiary. Their marriage might have been short-lived; when Else caught diphtheria the year after their wedding, Behring's antitoxin saved her life, and together, they went on to have seven children.

GIFT OF LIFE On Christmas Eve of 1891, Behring injected diphtheria antitoxin into an eight-year-old boy with severe diphtheria, and he later made a full recovery. Although the role of antibodies as the specific therapeutic agent in serum therapy was not known to Behring and his colleagues, evidence for the efficacy of serum therapy was irrefutable; in the succeeding decade, the 50% mortality rate of diphtheria plunged to 13%. Even Rudolf Virchow, a skeptic of the humoral theory of immunity, admitted that "theoretical considerations must give way before the brute force of figures, which are so expressive as to defy contradiction."

HORIZONS For a time, Behring's discovery perpetuated a misunderstanding of the immunologic basis of disease. Since the time of Hippocrates, medicine had espoused the humoral basis of immunity. The theory of cellular immunity developed much later, and was first proposed by Elie Metchnikoff in 1884. By demonstrating the immune properties of cell-free blood serum, Behring's work dealt a heavy blow to proponents of cellular immunity. Although Metchnikoff was later recognised with the Nobel Prize in 1908, his theory of cellular immunity as the second arm of the immune system would not be widely accepted until the mid-twentieth century.

Research on a new diphtheria vaccine was Behring's last major scientific project before the outbreak of World War I. The new methods of trench warfare that the war inaugurated led to devastating wounds that were highly susceptible to tetanus infection. For the first time, tetanus serum was injected prophylactically on a large scale. Behring was involved with determining the appropriate doses for prophylaxis and finding ways to enhance the output of the crucial antitoxin. Behring also remained a professor at the University of Marburg for the rest of his life.

DOCTORS AND DEUTSCHMARKS Behring's unabashed pursuit of financial rewards for his efforts—unusual in that era—drew much criticism. One of the first modern medical entrepreneurs, he aggressively sought to patent his discoveries, and profited handsomely from their applications. This conflicted with the more genteel notions that prevailed at the time, which venerated physicians as selfless servants of mankind. The story of his selection for the Nobel Prize in the *Journal of the American Medical Association* noted that he had patented his diphtheria serum in the United States in 1898, which was decried as evidence of Behring's selfishness. Behring realised early in his career that private finance could help bring his discoveries to fruition. In 1895, he entered into an agreement with the Hoechst Dye Corporation to develop and market his diphtheria antitoxin. When he signed his agreement with Hoechst, his preparations were too variable and unreliable for commercial distribution. Fearing that French scientists would soon overtake them, Behring called on the experience of fellow scientific luminary, Paul Ehrlich to improve upon his technique. Ehrlich hoped to create a research institute of his own, and agreed to forfeit his share of the profits in exchange for Behring's guarantee of assistance with this endeavour. Behring did not carry out his part of the deal, but did keep his outsized share of the profits.

PARTING WAYS For all his accomplishments, Behring was a deeply troubled man. He suffered from frequent bouts of profound depression, and was institutionalised several times. His biographer, Derek Linton speculated that he kept busy to keep his internal demons at bay. A man of volcanic temper, he was known to unleash vitriolic diatribes against those with whom he disagreed. In 1913, Behring broke his femur. The bone never fully healed and shortened significantly. He suffered constant pain from the associated osteoarthritis and came to rely on narcotics for relief. In 1916, he developed a severe abscess that required surgical drainage. In his final months, he was mostly bedbound and morbidly depressed. The great discoverer of serum therapy died of pneumonia in Marburg on March 31, 1917. Despite the schism between Germany and her enemies during World War I, the British and American press made note of his passing.

BIBLIOGRAPHY

- Dubiski S. von Behring. JAMA 2006; 295:2539-40.
- Hanrahan CF. Who was Emil von Behring? Biologist (London) 2001; 48:136-7.
- Linton DS. Emil von Behring: Infectious Disease, Immunology, Serum Therapy. Philadelphia: American Philosophical Society, 2005.
- Loudon I. Western Medicine: An Illustrated History. New York: Oxford University Press, 1997.
- Magner LN. A History of Medicine. 2nd ed. Boca Raton: Taylor and Francis, 2005.
- McGrew RE, McGrew MP. Encyclopedia of Medical History. New York: McGraw-Hill, 1985.
- Raju TN. Emil Adolf von Behring and serum therapy for diphtheria. Acta Paediatr 2006; 95:258-9.
- Sigerist HE. The Great Doctors: A Biographical History of Medicine. Freeport: Books for Libraries Press, 1971.
- Simmons J. Doctors and Discoveries: Lives that Created Today's Medicine. Boston: Houghton Mifflin, 2002.
- Winau F, Winau R. Emil von Behring and serum therapy. Microbes Infect 2002; 4:185-8.