

Emil von Behring (1854–1917)

Emil von Behring researched treatments for the common childhood disease diphtheria in Germany in the 1890s and early 1900s. Diphtheria is a lethal disease that infected approximately 40,000 people in Germany between 1886 and 1888 with a general mortality rate of twenty-five percent. Behring investigated treatment of diphtheria using serum therapy, which is an alternative to vaccination that uses protective agents from other people's blood to defend a patient against disease. Behring termed those protective agents antitoxins. He received the first Nobel Prize in Physiology or Medicine for his work on serum therapy, which was one of the first Nobel Prizes given in the field of immunology. Additionally, Behring researched active vaccination as another way to protect patients from diphtheria. Behring's studies lowered the mortality rate of diphtheria in Germany through serum therapy and vaccination, especially since vaccination confers protection to both mother and infant during pregnancy and after birth.

Behring was born Emil Behring on 15 March 1854 in Hansdorf, West Prussia, or Poland as of 2022, to Auguste and August Behring. His father was the village schoolmaster. According to Derek Linton, a professor of history at Hobart and William Smith Colleges, Behring grew up in a patriarchal household where his father made most of the decisions for the family. Behring had twelve other siblings, which led to financial struggles, according to Linton. His father relied on teaching and farming to support the large family. Behring came from generations of village teachers, and, as such, he began receiving education from a young age. He attended the municipal school in Deutsch-Eylau, West Prussia, followed by secondary school in Hohenstein, West Prussia, starting in 1866. There, Behring received an education in history, physical sciences, mathematics, ancient and modern languages. According to Linton, when his parents could no longer afford to fund his tuition, Behring's teachers provided him with free board and tuition in commendation of his intellectual ability. In 1874, Behring passed his exams and graduated from secondary school.

From 1874 to 1878, Behring studied at the Academy for Military Doctors at the Royal Medical-Surgical Friedrich-Wilhelm-Institute in Berlin, Germany, where he earned his doctoral degree in medicine. During that time, Behring became involved in research, specifically with infectious diseases. He studied iodine-containing compounds such as iodine trichloride, which scientists at the time used for its antibacterial properties. From 1877 to 1878, Behring completed his doctoral thesis at Charité Hospital in Berlin on neuro-ophthalmology, which is the study of vision issues related to the nervous system. He received instruction and mentorship from ophthalmologists such as Carl Ernst Schweigger and Wilhelm Uhthoff. After obtaining his degree, Behring passed an examination in 1880 that allowed him to practice medicine locally. In return for covering Behring's educational expenses, the military required him to serve one year as a military surgeon for each semester of school. Therefore, from 1881 to 1883, he worked in the Second Hussar Regiment in Posen, Poland, as an assistant physician.

Following his military service, Behring served at the Pharmacological Institute at the University of Bonn in Bonn, Germany, in 1887 and the Army Medical College in Berlin in 1888, where he started to research serum therapy. Researchers in the late 1800s defined serum as a component of the blood that contained antibacterial properties. As of 2022, researchers recognize that what protects against bacteria is a type of cell within the blood called an antibody, rather than a property of the blood itself. Unlike vaccination, which stimulates a person's immune system to produce its own antibodies, serum therapy is the transfer of serum antibodies from an individual who already had the disease. Behring was one of the first scientists to observe that serum had protective properties against disease and conduct research on serum therapy. In Bonn, he applied serum research to bacterial immunology, which is the study of how the immune system fights bacterial infections.

In 1889, Behring moved to the Hygiene Institute of Berlin and worked as an assistant to Robert Koch. Koch researched tuberculosis, a bacterial disease that damages the lungs, and his institute was one of the largest research centers for bacteriology in Germany in the late nineteenth century. Behring built upon his previous work with antibacterial resistance in serum and applied that to diphtheria therapy. Diphtheria is an infection caused by the bacteria *Corynebacterium diphtheriae*. At the time, diphtheria often led to death in children, as the disease causes the formation of a thick, gray substance in the throat, which obstructs breathing and results in suffocation. Koch's other student, Shibasaburo Kitasato, worked closely with Behring on serum therapy at the Hygiene Institute since they both researched bacterial infections. However, Kitasato researched tetanus, a lethal disease that caused maternal and neonatal death at the time.

In 1890, Behring and Kitasato published "Ueber das Zustandekommen der Diphtherie-Immunität and der Tetanus-Immunität bei Thieren" (The Mechanism of Immunity in Animals to Diphtheria and Tetanus). Behring noticed that when he injected diphtheria bacteria into rats, guinea pigs, and rabbits, their blood could neutralize the toxin after they fought the disease. Additionally, when he transferred the serum from those immunized animals into non-immunized animals, the second group of animals also received protection against the disease. From those experiments, Behring deduced that there must be a molecule in the immunized animals' sera that conferred protection, thus coining the term antitoxin. As of 2022, researchers and physicians use the term antibodies instead. The phenomenon that Behring observed was an example of passive immunization, which is where an individual is protected from disease with someone else's antibodies. Passive immunization differs from active immunization, which is when vaccines stimulate the body's immune system to produce its own antibodies.

In 1891, Behring and his colleagues treated one of the first child patients with diphtheria serum therapy in Berlin. They tested the use of antitoxic serum in children and adults over the next few years, but the human trials were not effective due to low-quality serum. In 1894, Paul Ehrlich, who was one of Behring's colleagues at Koch's Hygiene Institute, published the results of one of the first applications of serum therapy to official human clinical trials. Ehrlich used Behring's concept of serum therapy but improved it by using larger animals and higher quality serum. Serum therapy for diphtheria successfully cured approximately seventy-seven percent of patients in the trial, contributing to the overall reduction in diphtheria mortality in Germany by fifty percent that year. However, despite its role in alleviating the diphtheria crisis, Behring's serum therapy also had harmful side effects. In 1896, a child died because the child's body registered the serum from serum therapy as a foreign substance, triggering a severe and fatal immune response.

In 1894, Behring left the Hygiene Institute and transitioned into a career in academia. With the help of Friedrich Althoff, who was a departmental director in the Prussian Ministry of Education, Behring became Professor of Hygiene at the University of Halle in Halle, Germany. According to Linton, the faculty at Halle criticized Behring's lack of preparedness and incompetence in the instruction of hygiene lectures, which are lessons on infectious disease prevention. In 1895, Althoff helped Behring secure another position at the University of Marburg as Professor of Hygiene and Director of the Hygienic Institute in Marburg, Germany. Despite faculty opposition, Behring and Althoff used their administrative power to override and force Behring's appointment at the university according to Linton. Linton also reports that over the semester, Behring improved his teaching and earned the respect of students and staff, securing his position as professor until his retirement in May 1916. Also in 1895, Behring requested a United States patent for his diphtheria antitoxin serum technology in horses, which he received three years later.

In 1896, Behring married Else Spinola, the daughter of the administrative director of the Charité Hospital, where Behring had completed his doctoral thesis. Else contracted diphtheria in 1897, but Behring's serum therapy saved her life. The couple had six sons. According to one son, Behring had little involvement in the upbringing of his children.

Behring established his own manufacturing firm, Behringwerke, in Marburg in 1904. He collaborated with Carl Siebert, a previous colleague who conducted tetanus serum research, to construct the firm. The Behringwerke facilities consisted of a research laboratory and a large field that housed experimental animals such as cows and horses. Unlike his laboratory at Koch's Hygiene Institute, Behring used funding from his awards to equip Behringwerke with advanced technology, such as

high-resolution microscopes and power centrifuges. Behring directed most of the firm's activities, which centered on the production of tetanus serum and tuberculosis vaccines. Behringwerke became one of the first biomedical firms run by a scientist.

In the early 1900s, Behring turned his focus to researching antitoxin-toxin complexes as a type of active immunization. Active immunization is the use of vaccines to stimulate the body to produce its own antitoxins to fight disease. Following Behring's previous work on serum therapy, other scientists showed that serum transfer did not provide long-term immunity as it had an efficacy time frame of only two to three weeks. Therefore, scientists turned to active immunization techniques since the production of the body's own antitoxins would provide longer-lasting immunity. However, injecting pure toxin into patients to stimulate antitoxin production would likely be toxic and lethal. Therefore, Behring experimented with making complexes of diphtheria toxin that were subdued by diphtheria antitoxin as a way to vaccinate patients in a safe manner.

In 1913, Behring published "Ueber ein neues Diphtherieschutzmittel 1" (About a New Protective Remedy Against Diphtheria), a paper on a vaccine called diphtheria AT, or antitoxin-toxin complex. His paper detailed how injecting the diphtheria AT vaccine into the body stimulated the immune system to generate antitoxins but would not harm the vaccinated individual. He also wrote about how the antitoxins produced by the person's own body could provide long-term protective immunity, unlike serum therapy. Subsequent clinical trials supported Behring's findings. One study found that less than one percent of vaccinated infants contracted diphtheria. However, the diphtheria AT vaccine costed too much to manufacture on a large scale. In addition, the onset of World War I in 1914 shifted public focus away from the diphtheria vaccination efforts and toward wartime activities, according to Stefan H. E. Kaufmann, a researcher who studied immunology and its history in Germany in the late twentieth century. Despite the decreasing public focus on vaccination, the products of Behring's research continued to protect the people of Germany from diseases like diphtheria.

In 1901, Behring was awarded the first Nobel Prize in Physiology or Medicine for his research on the diphtheria antitoxin and serum therapy. That same year, the Prussian government bestowed Behring with hereditary nobility, which is an honorary title that passed along to his descendants, granting him the title Emil von Behring. Although passive immunization using serum is not common as of 2022, Behring's investigations on antitoxins contributed to the understanding of how the immune system defends the body from disease. According to Google Scholar in 2022, over 900 publications have cited Behring's 1890 paper on diphtheria serum therapy.

The molecules that Behring had called antitoxins continued to undergo further study by Ehrlich, Behring's former colleague. Ehrlich renamed these molecules antibodies and found that they were integral to the body's defense to infections, as well as the body's ability to fight the infections if encountered later in life. In addition, Gaston Ramon, a researcher who studied diphtheria and tetanus in France, built upon Behring's studies on active immunization and vaccine development. Ramon devised a diphtheria and tetanus vaccine by inactivating the toxin with formaldehyde, allowing for mass vaccine production with greater efficacy. As of 2022, the diphtheria vaccine administered is DTaP, which first came about in the 1940s and protects against diphtheria, tetanus, and pertussis, also called whooping cough. In 2016, more than eighty percent of children in the US had received DTaP vaccinations, and vaccination is mandatory for most elementary and secondary schools in the country. Behring advanced the understanding of the human immune system, allowing future immunologists to better utilize the body's immune system to combat disease.

Behring died at age 63 on 31 March 1917 in Marburg, Germany after a short respiratory illness.

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