MILESTONES

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MILESTONE 1

"Blood is a very unusual fluid"

The history of antibodies is intrinsically linked with that of vaccines. Evidence of variolation—the practice of exposing healthy people to tissue from people infected with smallpox as a way to prevent infection—dates back to the 10th century in China, but the method became famous thanks to the work of Edward Jenner. In 1796, Jenner inoculated pus extracted from a pustule of a cow infected with cowpox and injected it into the arm of an 8-year-old boy, then demonstrated that this conferred protection from smallpox. This inspired subsequent work, including work by Louis Pasteur, who developed a human vaccine against rabies in 1885. However, it was not until two articles were published in 1890 that the mechanism of the protection afforded by vaccination began to be understood.

Publishing in the *Deutsche Medicinische Wochenschrift*, Emil Behring and Shibasaburo Kitasato described "[t]he mechanism of immunity in animals to diphtheria and tetanus," explaining how infected animals could be cured and healthy animals could be pretreated to prevent infection. Although the article did not explain how animals were immunized, it reported that blood removed from the carotid artery of immunized rabbits and allowed to stand until serum formed could then be transferred into the abdominal cavity of mice to confer protection against subsequent challenge with either tetanus bacilli or tetanus toxin. Furthermore, the serum could be injected therapeutically to rescue infected mice from the lethality of tetanus. Importantly, control blood and serum from non-immune animals did not transfer protection. In a follow-up article, Behring described a similar mechanism by which blood or serum taken from rats rendered immune to diphtheria toxin was sufficient to protect guinea pigs from sickness induced by a subsequent injection of the same toxin. Collectively, the articles demonstrated that the serum of immune animals is capable of neutralizing toxins; that this property is exclusive to immune animals; and that serum can be used to both prevent infection and treat infection.

Notably, the discovery that cell-free serum was sufficient to transfer protection against toxins contrasted with the view of cellular immunity as the first line of defense against infection, which included the concept of phagocytosis formulated by Élie Metchnikoff just a few years earlier, and it fuelled the ongoing dispute between cellular and humoral immunologists. Nonetheless, with the help of Paul Ehrlich (MILESTONE 2), who would later go on to cement the key role of serum antibodies in protective immunity, Behring was able to devise a strategy to produce anti-diphtheria serum at a sufficiently large scale and by a reproducibly standardized method to be used to treat human infections. This work formed the basis of the first Nobel Prize in Physiology or Medicine, awarded in 1901 to Behring "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 deaths." Therefore, the work of Behring and Kitasato not only proved that indeed "[b]lood is a very unusual fluid," it also represented a major step in the discovery of antibodies, the development of effective human vaccines and the birth of immunology.

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ORIGINAL RESEARCH PAPERS Behring, E. & Kitasato, S. Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren. *Dtsch. Med. Wschr* **16**, 1113–1114 (1890) | Behring, E. Untersuchungen über das Zustandekommen der Diphtherie-Immunität bei Thieren. *Dtsch. Med. Wschr*. **16**, 1145–1147 (1890)
FURTHER READING de Kruif, P. *The Microbe Hunters* 2nd edn. (Harcourt, Brace and Jovanovich, San Diego, 1954) | Emil von Behring—Facts. Nobel Media AB 2014 http://www.nobelprize.org/nobel_prizes/medicine/laureates/1901/behring-facts.html (13 September 2016).