MILESTONE 4

Serum power

Monoclonal antibody therapy is a cornerstone of modern care for non-communicable diseases, including cancer, autoimmune diseases and cardiovascular diseases. But long before the identification, isolation or cloning of antibodies, passive transfer of immune sera was used as a treatment for infectious disease — specifically tetanus and diphtheria — which were otherwise frequently lethal. Today still, antiserum from convalescent donors is being explored as a potential therapeutic intervention against viral infections, including those caused by ebolavirus and by pandemic SARS-CoV-2.

Yet the therapeutic potential of immune sera was first demonstrated more than 100 years ago in a series of animal experiments assessing immunity to the bacterial pathogens *Clostridium tetani* and *Corynebacterium diphtheriae* and their respective toxins. In 1890, Emil von Behring and Shibasaburo Kitasato reported that whole blood or cell-free serum from a rabbit previously injected with *C. tetani* could protect mice infected with a lethal dose of tetanus bacilli. Moreover, pre-treating tetanus toxin-containing bacterial filtrate with serum from an immunized rabbit blocked its lethality when it was subsequently injected into mice. Their landmark conclusions included that: cell-free components of the blood of a tetanus-immune rabbit had properties that could destroy the toxin; these properties were lacking in the blood of tetanus-naive animals; the tetanus-inactivating components were stably transferrable to *C. tetani*-infected animals via transfusion, in which they exerted a therapeutic effect.

> “serum therapy is the foundation of … antibody-based immunotherapy”

One week after the report of these results, Behring published a related paper analysing immunity to *C. diphtheriae* in animals in which he demonstrated that transfer of antisera from immunized rats protected guinea pigs injected with diphtheria toxin. These findings set the stage for what came to be called serum therapy — the transfer of sera from an immunized donor to a naive recipient to treat an infectious disease — and for which von Behring was awarded the very first Nobel Prize in Physiology or Medicine in 1901.

In 1894, the success of serum therapy in humans was first reported in children with diphtheria, a disease that accounted for 1% of all deaths of children under the age of 5 years at the time. When treatment with antisera was initiated early after diagnosis, nearly 100% of children recovered. Shortly thereafter, prevention of tetanus was achieved using horse antisera, which became a mainstay therapy of wounded soldiers during the First World War to prevent what had previously been a lethal disease. These successes with passive serum therapy also served to galvanize the research community to develop vaccine strategies that would actively elicit the protective antibodies generated naturally during infection.

The discovery that immunization with a bacterial pathogen or product could elicit a substance in serum with toxin-neutralizing properties — and which we now know to be antibodies — provided some of the first insights into humoral immunity that could account for the results of vaccination, as observed by Edward Jenner 100 years previously (MILESTONE 2). Elucidating the effects of antisera contributed to an understanding of hypersensitivity (observed owing to the use of animal antisera in humans) and the development of active vaccination for infectious disease. The demonstration of therapeutic efficacy using serum therapy is the foundation of today’s antibody-based immunotherapy.

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ORIGINAL ARTICLES Behring, E. & Kitasato, S. Ueber das Zustandekommen der Diphtherie-immunität und der Tetanus-Immunität bei Thieren. *Dtsch. Med. Wochenschr.* **49**, 1113–1114 (1890) | Behring, E. Untersuchungen über das Zustandekommen der Diphtherie-Immunität bei Thieren. *Dtsch. Med. Wochenschr.* **50**, 1145–1147 (1890)

FURTHER READING Kaufmann, S. H. E. Remembering Emil von Behring: from tetanus treatment to antibody cooperation with phagocytes. *mBio* **8**, e00117-17 (2017) | Kaufmann, S. H. E. Emil von Behring: translational medicine at the dawn of immunology. *Nat. Rev. Immunol.* **17**, 341–343 (2017)