

In 1890, Emil Behring and Shibasaburo Kitasato reported an extraordinary experiment. They immunized rabbits with tetanus and then collected serum from these animals. Subsequently, they injected 0.2 ml of the immune serum into the abdominal cavity of six mice. After 24 hours, they infected the treated animals and untreated controls with live, virulent tetanus bacteria. All of the control mice died within 48 hours of infection, whereas the treated mice not only survived but showed no effects of infection.

This landmark experiment demonstrated two important points. One, it showed that following immunization, substances appeared in serum that could protect an animal against pathogens. Two, this work demonstrated that immunity could be passively acquired. Immunity could be transferred from one animal to another by taking serum from an immune animal and injecting it into a non-immune one. These and subsequent experiments did not go unnoticed. Both men eventually received titles (Behring became von Behring and Kitasato became Baron Kitasato). A few years later, in 1901, von Behring was awarded the first Nobel prize in Medicine.

These early observations and others paved the way for the introduction of passive immunization into clinical practice. During the 1930s and 1940s, passive immunotherapy, the endowment of resistance to pathogens by transfer of the agent of immunity from an immunized donor to an unimmunized recipient, was used to prevent or modify the course of measles and hepatitis A. During subsequent years, clinical experience and advances in the technology of preparation of immunoglobulin for passive immunization have made this approach a standard medical practice. Passive immunization based on the transfer of antibodies is widely used in the treatment of immunodeficiency diseases and as a protection against anticipated exposure to infectious agents against which one does not have immunity.

Immunoglobulin for passive immunization is prepared from the pooled plasma of thousands of donors. In effect, recipients of these antibody preparations are receiving a sample of the antibodies produced by many people to a broad diversity of different pathogens. In fact a gram of intravenous immune globulin (IVIG) contains about  $10^{18}$  molecules of antibody

(mostly IgG) and may incorporate more than  $10^7$  different antibody specificities. During the course of therapy, patients receive significant amounts of IVIG, usually 200–400 mg per kilogram of body weight. This means that an immunodeficient patient weighing 70 kilograms would receive 14 to 28 grams of IVIG every 3 to 4 weeks.

A product derived from the blood of such a large number of donors carries a risk of harboring pathogenic agents, particularly viruses. The risk is minimized by the processes used to produce intravenous immune globulin. The manufacture of IVIG involves treatment with solvents, such as ethanol, and the use of detergents that are highly effective in inactivating viruses such as HIV and hepatitis. In addition to removing or inactivating infectious agents, the production process must also eliminate aggregated immunoglobulin, because antibody aggregates can trigger massive activation of the complement pathway, leading to severe, even fatal, anaphylaxis.

Passively administered antibody exerts its protective action in a number of ways. One of the most important is the recruitment of the complement pathway to the destruction or removal of a pathogen. In bacterial infections, antibody binding to bacterial surfaces promotes opsonization, the phagocytosis and killing of the invader by macrophages and neutrophils. Toxins and viruses can be bound and neutralized by antibody, even as the antibody marks the pathogen for removal from the body by phagocytes and by organs such as liver and kidneys. By the initiation of antibody- dependent cell-mediated cytotoxicity (ADCC), antibodies can also mediate the killing of target cells by cytotoxic cell populations such as natural killer cells.

*(Adapted from Kuby Immunology's Clinical Focus)*

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