History of Immunoglobulin Replacement

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• Immunoglobulin • IVIg treatment • Primary immunodeficiency
• Antibody deficiency • Immune modulation

HISTORY OF IMMUNOGLOBULIN TREATMENT

In 1890, von Behring and Kitasato[1] proved that ''bloodserum'' of rabbits immunized with tetanus toxin contained activity against ''tetanus poison,'' and such blood serum transferred to rabbits protected these normal (naive) animals against tetanus. In 1901, von Behring was awarded the first Nobel Prize in Medicine or Physiology for his work in this field. Ehrlich[2] demonstrated that protection could be quantitatively correlated to the amount of antitoxin in the blood.

In 1910, Dr. A. Wolff-Eisner, a 33-year-old physician in Berlin, published ''Curative Serum Therapy and Experimental Therapy,'' a handbook for clinic and medical practice.[3] His intention—not so far from our own current intentions—was to convey to clinicians and practitioners ''the advances of biological science as they relate to therapy. The theoretic [the science] should only be included as far as necessary for the understanding of treatment.'' Several infectious diseases and conditions such as allergy and cancer were treated with curative serum. Serum therapy of diphtheria and tetanus was already common practice.[4]

In Germany alone, five companies, including Höchster Farbwerke, Merck-Darmstadt, and Behring-Höchst, produced curative serum; products from Schering and Parke-Davis were also available. There was international cooperation: Calmette[5] in Lille, France worked on the treatment of snake venom; Wolff-Eisner in Berlin concentrated on serum therapy of hay fever and treatment of bacterial diseases. Serum therapy was introduced in the treatment of staphylococcal disease (van de Velde, Holland), streptococcal infection (R. Freund, Berlin), and meningococcal disease (Flexner, New York).[6–8] Curative (mainly antitoxic) sera were produced in different animal species because serum sickness already was recognized as one of the feared complications of therapy. Convalescent human sera had great advantages compared

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with sera of immunized animals, because human serum could be applied without the risk of anaphylaxy and serum sickness.

In 1907, Cenci[9] (Italy) applied convalescent human sera for the prevention of measles. McKhann and Chu[10] followed in the same indication with material obtained from the globulin fraction of placenta in 1933. Treatment with curative sera was performed successfully and saved the lives of many individuals in the first third of the twentieth century,[5] mainly children with diphtheria and soldiers with tetanus in World War I. Treatment was also widely applied in pneumococcal disease.

Although antibody treatment had been widely used,[11] information on serum protein composition was incomplete until the 1930s. The proof that antibodies localized to the immunoglobulin (Ig) compartment of human serum came in the 1930s. Initially fractionation was performed by precipitation with different salt concentrations (such as ammonium sulfate).

In 1938, Karelitz,[12] an associate of Schick, published prophylaxis against measles with the globulin fraction of immune adult serum in *The American Journal of Diseases of Children*, but profound understanding on serum proteins became available only after Tiselius and Kabat[13] published their pioneering work on electrophoresis of immune serum in *Science* in 1938. Just 2 years later, Cohn and his group[14,15] reported on preparation and properties of serum and plasma proteins, which opened the way for Ig prophylaxis and treatment of infectious diseases.

Fractionation of Serum Proteins

Techniques developed by Cohn and his coworkers[14,15] in Boston at the beginning of World War II led to the development of the separation of plasma proteins into individual stable fractions with different biologic functions. The basis for Cohn's fractionation was to use low concentrations of alcohol by reducing the pH and lowering ionic strength. The procedure was performed at low temperature, which reduced the likelihood of contamination and made large-scale fractionation possible. This method, further refined in cooperation with J.L. Oncley,[15] is basically still in use and, with some additional steps, yields Ig for intramuscular and subcutaneous use. By the mid-1940s, however, Cohn[14] realized that an Ig product that could be applied intravenously was desirable. He recognized that the removal of depressor substances was necessary and would require new technology.

In the following years, numerous cooperations were established between Cohn and others,[16] including Elliot Robinson at the Massachusetts Antitoxin and Vaccine Laboratory, Charles Janeway[17] (Sen.) and John Enders at Harvard, and clinical trials to prevent viral diseases (eg, measles and hepatitis) were initiated. Because of the limited availability of blood, Ig products were also prepared from placentas. During and after World War II, the supply of gammaglobulin increased as plasma from the American Red Cross became available.

The first Ig products were mainly given to prevent and treat infections: polymyelitis, measles, mumps, pertussis, and hepatitis A.[18,19] These Ig disappeared as soon as the respective diseases could be and were prevented by vaccination. Other Ig products with defined specificities were developed subsequently and continue to be used currently (eg, tetanus Ig,[20] RHo(D) Ig,[21] rabies Ig, hepatitis B Ig,[22] and varicella zoster Ig[23]). Respiratory syncytial virus hyperimmunoglobulin[24] was licensed but later replaced by a respiratory syncytial virus monoclonal antibody,[25,26] one of the few monoclonal antibodies that made its way into clinical application in the prevention of an infectious disease—pneumonia caused by respiratory syncytial virus, a dangerous, potentially fatal disease in premature infants and newborns.