Immunotherapy in Clinical Medicine: Historical Perspective and Current Status

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KEYWORDS

• Immunotherapy • Vaccination • Immunoglobulins • Cytokines

Key Points

- The use of immunotherapy crosses disciplines and involves several diseases.
- Active immunotherapy in the form of vaccines remains the single most significant intervention in decreasing childhood mortality.
- The use of immunotherapy for the modulation of immune responses in noninfectious diseases is now the standard of care.

INTRODUCTION

Immunotherapy is broadly defined as the prevention and/or treatment of diseases by inducing, enhancing, or suppressing immune response, and has been recently reviewed in the context of biological disease modifiers.[1]

The concept of inducing protection against diseases dates back to the eighteenth century, before the germ theory of disease was scientifically proved. When microbiological methods to cultivate various organisms became available, methods to render these organisms nonpathogenic while maintaining immunogenicity made it possible to control and/or eradicate several acute and potentially fatal childhood infectious diseases. This active immunoprotection by routinely used vaccines has made the most significant contribution to the current status of human health and longevity.

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Passive immunotherapy, in the form of serum from recovering patients, was used even before the availability of antimicrobial therapy in the mid 1940s and was further improved by the use of antitoxins raised in animals. In 1944, the fractionation of human immunoglobulin for the treatment of measles overcame the problem of serum sickness and introduced the concept of pooled immunoglobulin therapy. Molecular technology has now offered development and the use of defined monoclonal antibodies against factors involved in the pathogenesis of diseases.

Immunotherapy has become an integral part of clinical practice. Articles that follow in this issue discuss the use of immunotherapy in various organ system disorders.

ACTIVE IMMUNOTHERAPY: VACCINATION

Active immunotherapy has been in use over the past 2 centuries to prevent the morbidity and mortality associated with various infectious diseases. Smallpox, a disease of the past, was a major killer in the eighteenth century. In 1796, Edward Jenner discovered that deliberate infection with the cowpox virus caused mild disease and, thereby, resulted in subsequent immunity to the smallpox virus infection. This discovery was a pioneering work in immunotherapy and also one of the greatest revolutions in medical therapy.[2,3] Vaccination (Latin: *vacca*, cow) was so named because the first vaccine was derived from a virus affecting cows. Using the same concept, effective vaccines in the form of either killed or attenuated pathogens have been developed for several infectious diseases (**Table 1**).

Louis Pasteur and coworkers first adopted the concept of physical attenuation of pathogenic organisms for the purpose of immunization in the early twentieth century. The concept came from an observation Pasteur made in 1881. A culture of *Pasteurella multocida* lying on his bench over the summer break failed to cause disease when injected into chickens. These chickens did not develop disease after a challenge with a newly made culture either. This finding led Pasteur[4] to the conclusion that the chickens were immune to the disease because of the previous exposure to aged and, probably, damaged culture. The physical attenuation of the organisms led to the discovery of vaccines against anthrax and rabies. Pasteur exposed *Bacillus anthracis* to oxygen before using it for vaccinating animals. He produced the first vaccine for rabies by growing the virus in rabbits and then weakening it by drying the affected nerve tissue.

In 1907, Calmette and colleagues[5] used passage in artificial media to attenuate *Mycobacterium bovis*, and in 1937, Theiler and Smith[6] used passage in mice and chick embryos to attenuate yellow fever virus before its use in human vaccines. In the middle of the twentieth century it was discovered that passage through cell culture was also a means of attenuation, probably by fortuitous selection of mutants better adapted to replication in vitro than in the living host. This technique allowed the selection of mutants by isolation of single clones and incubation at temperatures below the normal temperature of the host. Thus, the period between 1950 and 1980 saw the development of numerous attenuated virus vaccines, including those for poliomyelitis, measles, rubella, mumps, and varicella.[7] The ability to mix RNA segments from attenuated strains with RNA-encoding protective antigens from circulating wild strains led to the discovery of the influenza virus and rotavirus vaccines.

The use of completely inactivated vaccines started in the nineteenth century and was initially directed against typhoid and cholera.[7] More recently, the Salk poliomyelitis and hepatitis A vaccines contained whole inactivated viruses.[7] The recognition of extracellular bacterial toxins resulted in Ramon developing immunogenic but nontoxic toxoids for diphtheria and tetanus.[7] Later it became possible to separate