

# Genesis and Evolution of Diagnostic and Clinical Immunology

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The spectacular success of *Clinical and Diagnostic Laboratory Immunology* as a relatively new journal indicates the maturation of immunology as an important component of medical science and practice. This essay reflects upon the birth and rapid development of diagnostic and clinical applications of immunology and draws some lessons for their future.

## DIAGNOSTIC IMMUNOLOGY

**Antibodies resulting from infection.** The discoveries of von Behring and Kitasato a century ago demonstrated that animals recovering from diphtheria or tetanus develop an antitoxin in their serum. It did not take long before the French investigator Widal realized that the appearance of antibodies itself serves as a diagnostic sign of recent infection. The Widal test for typhoid fever is based on the fact that, during the course of disease, antibodies to the causative agent rise in the serum. This rising titer of antibody provides valuable diagnostic information, especially when the isolation and identification of the causative agent are difficult, dangerous, or impossible. Thus, a comparison of acute- and convalescent-phase-serum titers is still the basis for diagnosis of many viral infections.

Another pathogenic organism difficult to cultivate is *Treponema pallidum*. Wassermann, Neisser, Bruck, and Schuch conceived the notion of employing Bordet's complement fixation reaction in the diagnosis of syphilis. Using a suspension of liver from a syphilitic patient as antigen, the test worked marvelously. Later, Landsteiner carried out a control experiment and used liver from a nonsyphilitic cadaver. Much to everyone's surprise, normal liver served as antigen in the syphilitic reaction, showing that the antibodies were directed to a normal tissue antigen as well as to the infectious organism. In fact, beef heart proved to be the best source of the antigen for syphilis serology.

**Antibodies to tissue antigens.** It took a number of years before the beef heart antigen of the Wassermann test was purified and identified as cardiolipin. The notion that antibodies are formed to tissue antigens of the host, however, disclosed an entirely new vista of diagnostic immunology. The demonstration of such antibodies to normal tissue antigens is the basis for the diagnosis of the autoimmune diseases. Thus, in lupus erythematosus, the presence of antinuclear antibodies is the primary step in laboratory confirmation of the disease. Even the precise specificity of the tissue antigen is useful diagnostically for sorting out subsets of disease; for example, antibody to snRNP is the diagnostic standard for mixed connective-tissue disease, and antibody to the centromeric protein is an important diagnostic sign for the CREST variant of scleroderma. Antibodies to thyroglobulin and thyroperoxidase are now commonly applied in diagnostic tests for chronic lymphocytic thyroiditis, while antibodies to islet cell antigens prove

to be increasingly valuable as early warning signs of impending type 1 diabetes. The demonstration of antibodies to tissue antigens has presently grown to be a major responsibility of the typical diagnostic immunology laboratory.

**Skin tests.** Some applications of diagnostic immunology are done on patients. Soon after the isolation of the tubercle bacillus, Robert Koch realized that patients with tuberculosis may develop a violent reaction to an extract of the microorganism. This observation evolved into a skin test, in which old tuberculin or the purified protein derivative is injected into the skin, where it produces a delayed hypersensitivity response, signifying recent or past contact with the tubercle bacillus. The delayed-type hypersensitivity reactions are still useful for some diseases, such as tuberculosis and histoplasmosis, in which cell-mediated responses are more informative than circulating antibodies.

Another application of the skin test is based on injection of a bacterial toxin. If antitoxin is present, the local redness induced by the toxin will be neutralized. This principle underlies the Schick test for diphtheria and the Dick test for scarlet fever. Although rarely used today, these tests show the important principle that antibody can neutralize bacterial toxins in the body.

**Antibodies as reagents.** Soon after the original publications of von Behring and Kitasato, Gruber and Durham showed that antiserum could agglutinate the corresponding bacterial cells in the test tube. This finding led to an entirely new application of diagnostic immunology, i.e., the use of antibodies as highly specific laboratory reagents. The precise recognition and serotyping of many bacteria depend upon the availability of panels of reference antisera. The ability of known antibodies to neutralize viruses is a major tool in the identification of viral agents isolated from patients.

The application of antibodies as specific reagents has gone far beyond their use in the diagnosis of infectious diseases. The availability of specific immunologic reagents to cell surface alloantigens of erythrocytes or leukocytes enables the widespread use of blood transfusion and organ transplantation in medicine and surgery. Immunoassays are applied in all components of the modern diagnostic laboratory. The most sensitive assays for hormones, such as those used in pregnancy tests, depend upon potent antibodies. Many immunoassays for enzymes important in clinical chemistry and hematology employ specific antibodies. For these purposes, the availability of monoclonal antibodies developed from hybridomas has revolutionized the immunoassay and extended its use into many areas of science outside medicine.

## CLINICAL IMMUNOLOGY

In a strict sense, clinical immunology can be defined as immunology practiced at bedside. It also evolved from the pioneering investigations of von Behring and Kitasato. They were the first to show that it is possible to use antitoxins for treating diseases, such as diphtheria and tetanus, in which the major pathology is attributable to specific toxic products of the

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pathogens. Although now largely replaced by treatment with antimicrobial agents, passive immunization still finds a place in medical treatment of some bacterial and viral diseases. Thus, intravenous immunoglobulins, containing a mixture of antibodies to many common pathogens, convey protection against many infectious diseases.

Another, and somewhat unexpected, value of antibody therapy depends upon the regulatory value of antibodies. A major triumph of modern medicine has been the application of anti-Rho for the prevention of hemolytic disease of the newborn.

The availability of monoclonal antibodies and the opportunity to "humanize" antibodies have unlocked many opportunities for immunotherapy beyond its known applications in infectious diseases. Antibodies to lymphocytes, or more precisely, CD4-bearing T lymphocytes, have found a place in the prevention of transplant rejection.

Clinical immunology these days is largely concerned with the diagnosis and treatment of autoimmune diseases and with immunology-based therapies applied in the treatment of immune-mediated disorders. Antibodies to certain cytokines, such as tumor necrosis factor alpha, have been shown to benefit patients with inflammatory diseases, such as rheumatoid arthritis. Other cytokine inhibitors show promise for the treatment of autoimmune diseases.

Another striking event in current clinical immunology is the revival of interest in vaccines. Not only are new methods being developed to improve the safety and efficacy of existing vac-

cines against infectious diseases, but entirely new principles are evolving. For example, the use of DNA-based vaccines holds extraordinary promise for combining the values of a live vaccine with the safety of inactivated vaccines. Moreover, active immunization is being applied in many new ways; for example, one proposed treatment of autoimmune diseases is the use of vaccines to cell receptors of "pathogenic" T cells.

#### A GLIMPSE OF THE FUTURE

From the preceding discussion, it is clear that diagnostic immunology and clinical immunology have carved out a prominent place in the health care arena. The diagnosis of infectious diseases, the successful outcome of transfusions and transplants, and the availability of biochemical and hematologic assays with extraordinary specificity and sensitivity capabilities all attest to the value of antibody detection. Immunologic methods are used not only in the treatment and prevention of infectious diseases but in the large number of immune-mediated diseases. Yet, diagnostic immunology and clinical immunology have only begun to reach their full potential in medicine and public health. Each new advance in basic knowledge of immunology expands and extends our vision. Journals like *Clinical and Diagnostic Laboratory Immunology* will brighten the way as we enter the second century of medical immunology.

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*The views expressed in this Commentary do not necessarily reflect the views of the journal or of ASM.*