CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, July 1996, p. 369–370 Vol. 3, No. 4
1071-412X/96/$04.00+0

GUEST COMMENTARY

The Erwin Neter Memorial Lecture: Looking to the Future of Medical Laboratory Immunology, a Personal View

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Immunologic techniques have become very useful and important in the diagnosis of disease. Although many people regard immunology as a new science, it can be traced back to antiquity. Egyptian writings from 4,000 years ago describe severe epidemics, and two Greek historians, Thucydides and Procopius, recorded details of devastating plagues (Table 1). These historians noted that survivors of the disease were safe from further attack and could care for the sick. Procopius coined the term immunity, from the latin *immunitas*, which means exempt from service. The concept of immunity was also known in ancient China, where children were inoculated with fluid from the pustules of smallpox patients to protect them from the disease (4). The next step forward occurred in the late 18th century, when Edward Jenner used nonvirulent organisms for immunization and reduced the risk of the procedure. This is where we are today, designing vaccines to prevent serious infections. Successful immunization does prevent disease and can lead to eradication of the infecting organisms. We are indebted to Louis Pasteur, who postulated and proved the germ theory of disease; to Emil von Behring, who saw that antitoxins could be used to treat existing disease; to Ilya Metchnikoff, who realized the importance of phagocytosis and cellular immunity; and to Paul Ehrlich, who proposed the concepts of cellular receptors and autoimmunity.

The discipline of medical laboratory immunology is relatively new. When I began working in this field about 30 years ago, we did not have the reagents and techniques that are taken for granted now; we raised our own antibodies in rabbits, using antigens which we isolated ourselves. Sephadex and column chromatography, sucrose density gradients, and Spinco centrifuges were the workhorses. The detailed study of lymphocytes was in its infancy, and patient immunologic studies were limited to proteins in serum and urine and some skin tests. Decisions on the immune status of a patient were made on the basis of specific antibody titers and crude serum protein electrophoresis patterns. The concept of radial diffusion, developed by Mancini and her colleagues (2, 3) and by Fahey and McKelvey (1), had tremendous impact in the clinical laboratory. Suddenly it was possible to measure the levels of IgG, IgA, IgM, and any antigen in serum by a simple straightforward procedure. This technique quickly became indispensable and was, I believe, the impetus for the establishment of many diagnostic immunology laboratories. It was quickly realized that these were very useful laboratories; the data generated were applicable to many of the traditional specialties, in particular rheumatology, pediatrics, allergy, and hematology-oncology. The new immunology laboratories gradually absorbed other tests, especially those involving autoantibodies, serology, and lymphocyte assays, and the modern diagnostic immunology laboratory was born (Table 2).

Medical laboratory immunology is now an accepted subspecialty, with a Board (the American Board of Medical Laboratory Immunology [ABMLI]), an association (the Association of Medical Laboratory Immunologists [AMLI]), and a journal (*Clinical and Diagnostic Laboratory Immunology*). We owe a big debt to the individuals who have guided us through the past few years, especially Drs. Douglas, Escobar, Folds, Nakamura, Osterland, Penn, Rabin, and Rose. Through their efforts the diagnostic immunology laboratory has become an important component of the clinical laboratory. We are independent units with a reputation for excellence, and until recently the future seemed bright. Now, however, there are clouds on the horizon; changes in health care financing have altered the rules, and we must recognize this. Managed-care programs, which contract to provide a patient's medical care for a fixed amount of money per year, are forcing hospitals to compete for patients. These patients have to be accepted at a low, fixed price, resulting in serious budget problems, especially at academic centers. Clinical laboratories have traditionally been money earners, but the fee-for-service concept is no longer viable; laboratories are now cost centers and must revise their operations to produce test results for the absolute minimum cost. Some people worry that academic laboratories will be replaced by commercial laboratories. I believe that we can survive, but only if we change. Many academic centers have the traditional setup for an academic institution: separate laboratories for chemistry/hematology, microbiology, immunology, and transfusion medicine, plus independent laboratories in other departments. There are many directors (some M.D.s, some Ph.D.s), managers, and specialized technologists, which is an expensive and wasteful system. A unified laboratory with a single control structure would be more efficient. It would have a minimum of faculty and managers and be staffed with well-trained medical technologists, at a ratio of about one technologist per four to five occupied beds. This would permit condensation of the ancillary services while maintaining excellence and would keep costs to a minimum.

How would medical laboratory immunologists fit into this unified laboratory? As I see it, the key to the efficient operation of a laboratory is the knowledge base of the people involved. As immunologists, we have had to learn many different disciplines, so that both faculty and staff have a wide knowledge base and are comfortable with highly complex tests and instruments. I have noticed that immunology attracts people who like to think—who enjoy challenges. Such skills will always be needed, but we must not be complacent, we must become more knowledgeable. All of us, M.D.s, Ph.D.s, and technologists, should learn more skills and not be afraid of new and different

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TABLE 1. A short history of immunology

Historian or scientist	Date	Event
Thucydides	died 395 B.C.	Plague of Athens
Procopius	died 562 A.D.	Bubonic plague
Jenner	1798	Cowpox
Pasteur	1880	Germ theory of disease
Metchnikoff	1884	Cellular theory of immunity
von Behring	1890	Antitoxin therapy
Ehrlich	1897	Side chain theory and "*horror autotoxicus*"

ideas. In the future, we will be responsible for one part of the central laboratory and will be expected to help out when needed in other sections, so we must expand our horizons. We must continue to be open to new techniques and methods, especially the application of molecular diagnosis. There will be great opportunities for well-trained faculty and technologists who can diversify into new techniques and responsibilities. In this context, it is important for immunologists to understand the politics involved. Not only should we combine with the rest of laboratory medicine to form a unified laboratory, but the certifying boards must also combine, to form a unifying laboratory scientist board; perhaps it could be called the American Board of Laboratory Scientists. This is important to ensure that all branches of laboratory science work together efficiently.

What about the tests themselves? Most diagnostic immunology laboratories offer a wide variety of tests. At the University of Virginia, the diagnostic immunology laboratory handles about 2 to 3% of the workload of the clinical laboratories yet has 25% of the repertoire of these laboratories. Consequently, staff have to be familiar with many different test protocols and proficient in all of them. Just as the clinical chemistry laboratories have changed in the last few years with the arrival of multitrack analyzers, so the diagnostic immunology laboratories will change with the arrival of automated immunoassay analyzers. These instruments will promote the unification of the separate laboratories. We should welcome this development and actively seek combinations of test protocols which provide the most information for the least cost, sample, and effort. Thirty years ago, the Mancini test was spectacular new technology; today, very few laboratories use radial immunodiffusion because it takes too much time and has too many errors. Rate nephelometry is the system of choice, and the use of kappa- and lambda-light-chain levels limits the number of immunofixations that are needed.

TABLE 2. The field of interest of a medical laboratory immunologist

Lymphocyte phenotyping
Protein analysis
Autoantibodies
Serology
Tumor immunity
Allergy
Immunodeficiency
Tissue typing

What about a more specific test, such as the antinuclear antibody (ANA) test? The ideal test protocol would answer the questions: is the antibody present, and if so, is it diagnostically significant? We need an initial screen for the ANA test that is cheap, easy, and reliable and that gives rudimentary quantitation. Currently, the indirect immunofluorescent test fulfills this function, but a dipstick-type test which could be performed at the bedside, or in a physician's office, would be better. A weak positive in an older female would be ignored, but a weak or stronger positive in a young female would be followed up by identification of the specific antibody involved. The goal is to identify the precise target of the antibodies present, so that data can be provided to help the clinician manage the patient. This brings me to my final point: part of our job is to develop the necessary tests if they do not exist; where we do not have sufficient data, it is our responsibility to generate the information needed.

Tests are becoming more complex and increasingly involve molecular biology. We hear a lot about the use of amplification procedures and Southern blots to detect very low levels of infectious agents or minimal residual disease. Examples would be the use of the polymerase chain reaction in the detection of infection with *Mycobacterium tuberculosis* and the use of amplification techniques to follow the eradication of hepatitis B and C viruses in liver transplantation. These procedures are also used to define the HLA specificity of bone marrow transplant donors and recipients, so that the transplants will have a better chance of success. Another benefit of molecular biology is the ability to produce antigens and antigen fragments by recombinant technology. We should all be learning these new techniques and be ready to apply them in the laboratory.

Tests will be miniaturized, with complex procedures run on, and by, a silicon chip. The combination of molecular biology and computer technology will revolutionize our techniques. Immunologists will survive and prosper by being highly productive, by doing only the appropriate and necessary tests; they must be an integral part of a unified clinical laboratory and must lead the changes which are coming. I believe that the future of our field, medical laboratory immunology, is still very bright, despite the immediate clouds. We have been given a superb start; now we have to get down to it and do the work. It will be fun!

(This lecture was presented at the Eighth Annual Meeting of the Association of Medical Laboratory Immunologists, Vail, Colo., 11 August 1995.)

REFERENCES

1. **Fahey, J. L., and E. M. McKelvey.** 1965. Quantitative determination of serum immunoglobulins in antibody-agar plates. J. Immunol. **94:**84–90.
2. **Mancini, G., A. O. Carbonara, and J. F. Heremans.** 1965. Immunological quantitation of antigens by single radial immunodiffusion. Immunochemistry **2:**235–254.
3. **Mancini, G., J.-P. Vaerman, A. O. Carbonara, and J. F. Heremans.** 1964. A single-radial-diffusion method for the immunological quantitation of proteins. Prot. Biol. Fluids **11:**370–373.
4. **Silverstein, A. M.** 1993. This history of immunology, p. 21–41. *In* W. E. Paul (ed.), Fundamental immunology, 3rd ed. Raven Press Ltd., New York.