IMMUNODIAGNOSTICS

Editors
Ralph M. Aloisi
Jayson Hyun

IMMUNODIAGNOSTICS

Proceedings of a National Symposium held at the University of Hartford, West Hartford, Connecticut, July 6-9, 1982

Editors

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INTRODUCTION

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Immunodiagnostics has experienced a period of unprecedented growth which has benefited many aspects of health care. This success has generated an enthusiastic momentum which provides an incentive to further research, and production. Growth in industries related to immunodiagnostics have occurred in recent years creating demands which have had a ripple effect on education, instrumentation, research and medicine. However, the most dramatic changes have occurred in some of the major medical centers and universities represented at this conference - at these institutions immunodiagnostics has grown quantitatively and qualitatively.

However, the enthusiasm seen in many major medical centers relating to diagnostic immunology is not shared by all. Many, if not most hospitals, universities and medical centers have made feeble advances into this exciting field. In 1981, a very cautious opinion was expressed by the working group of the International Union of Immunological Societies and the World Health Organization on the current status of use and abuse of laboratory tests in clinical immunology. The report was published in WHO bulletin and in the December 1981 issue of the Journal of Clinical and Experimental Immunology. Their report described many of the "Hot" tests as having limited value and prospects of growth. Meanwhile, John Langen of the

Nichols Institute (1979), predicted that the U.S. market for ligand assay reagents alone would reach $387,000,000.00 by 1985. Why do we have such a disparity of opinions on immunodiagnostics?

Three factors seem of critical importance to this wedge which separates the "boosters" from "gloomers". First the definitions of immunodiagnostics and immunodiagnosticians remains vague and ill-defined. Certainly, even to the most casual observer, Immunology is a field where diversity and heterogeneity are the rule. A 1979 survey conducted by the American Association of Immunology and reported by Noel Rose demonstrated that no less than 23 specialties were represented with less than 3% from clinical pathology and laboratory medicine. Accordingly, this diversity and heterogeneity results in poor communication, unclear goals and varied needs.

The second factor which has led us to this position of uncertainty related to the clinician-laboratory relationship. This relationship often produces a synergism and objectivity which is beneficial to health care, however, increasingly we read, hear and see a growing lack of communication and a developing casualness which results in waste and abuse of laboratory expertise. Important data which details the attributes or shortcomings of new or old immunodiagnostic tests seem not to be reaching the ears of the clinician. This situation diverts resources and brings clinical laboratory data under scrutiny.

Thirdly, the immunodiagnostics laboratory has a special and somewhat unique relationship with industry. Unlike many areas of immunology and laboratory medicine, the immunodiagnostics laboratory relies almost exclusively on available commercial kits, reagents and instrumentation. This situation, while often advantageous, has put us in the unenviable situation of being, to a degree, dependent on the perceptions of industrial administrators. The profit motive often leads us toward solutions and answers to problems and questions which have not been asked while many demanding questions remain unanswered.

In closely reviewing our uncertain state of growth, it seems clear that the diversity of disciplines and individuals have made a intraprofessional and interprofessional communication a major obstacle for immunodiagnostics and a major reason for this conference and book. These proceedings bring

users, producers, educators and clinicians together to focus our energies on the issues which face us.

These proceedings represent the combined efforts of 17 emminently qualified contributors and a score of individual support staff. As editors, we have not made an effort to challenge the experimental design or the scientific basis of the contributors and have restricted our activities to review of style, grammar and usage. While it is impossible to appropriately recognize all of these individuals who have assisted in making this conference a success, it would be wrong not to thank Carol Stasiowski, Judith Yoczik, Beverly Aslin, the Immunology Staff at St. Francis Hospital and Medical Center and the Summerterm Office and the College of Arts and Sciences at the University of Hartford.

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ORCHESTRATION OF THE IMMUNOLOGY LABORATORY FOR DIAGNOSIS OF IMMUNOLOGIC DISORDERS

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Until now, physicians have occupied a central role in medicine, since they served as editors of medical events. That is, not only did they see, listen to and examine the patients, but they also ordered tests, sorted out the results, selected what they needed, arrived at a diagnosis, and prescribed therapy with monitoring of response. Physicians will continue in this capacity, but mind you, now, they are overwhelmed with laboratory data and expanding therapeutic protocols. I am suggesting that even though the therapists in the future will have central position, diagnosticians will, hopefully, begin to look to the laboratory to play a small role, and maybe an increasing role, in preparing interpretive and possibly Laboratory Aided Diagnostic (LAD) packages. However, the testing that should be done in the future ought to be designed along lines that make sense. Such as, in the case of immunology, can we put together packages that truly test some central component of immunobiology? It is evident that diseases of the immunologic system represent imbalance to the point that the patient suffers. With these thoughts, let's see how the laboratory could play a more advanced role in diagnosis, particularly with LAD packages.

To begin with, we laboratorians are being aided by automation of tests and computer storage of data which creates a "Lab Machine". Such a vast and rapid collection of data will enable us to use our laboratories as an orchestra for interpretative reporting. A brief review of the evolving concept of the "Lab Machine" may be helpful. One such "Lab Machine" is found in Wichita, Kansas. It is the home of one laboratory of Consolidated Biochemical (CBL) and also Wesley Medical Center. Both of these laboratories are highly computerized. The

division of CBL dealing with customer service is staffed by tech that shift from time to time into this spot so that everybody in the laboratory has the opportunity to answer questions coming in from all over the United States about what tests and batteries are available, what the normal range is for a particular test, and most importantly, what the price is. All hand test results are entered into the computer via a cathode ray tube (CRT). The SMAC is on-line to the computer as is the Radioimmunoassay laboratory. The Wesley Medical Center laboratory is also computerized, and the two laboratory computer systems are coupled together. In both laboratories, the results from the Clinical Immunology Division, qualitative or quantitative, are entered into the computer via a CRT.

Before we attempted this, however, there was considerable reservation by many of us, that we would lose control or feel unneeded since the computer would handle the data, or that our lack of typing skills would prevent us from utilizing the computer. As I will show you our decision to put everything into the computer, including interpretive statements on LDH/CPK isoenzymes, etc, has turned out to be the key to a successful "Lab Machine". The battery of tests designed to facilitate evaluation of B cell function, called an Immunologic Survey (Fig 1) includes 23 tests. It should be pointed out that all those tests on the Immunologic Survey are not performed in the Clinical Immunology Division. But because all of the data from all divisions of the laboratory is put into the computer, it is possible to capture any test result from the CRT screen. Thus, the data from other than the Immunologic Division can be incorporated into our Immunologic Survey Reports. Thus, we can generate an informed interpretative report. One useful concept of the "Lab Machine" is, the test does not have to be done in the department rendering the interpretive report. The tests can be done anywhere. Most of us practice the concept of "departmentized laboratories" but with the "Lab Machine" the interpreter does not care where the test is done, and cuts across all divisions of the laboratory and thereby, performs as an editor.

Figure 1. The Immunologic Survey is our first LAD package. It is alterable by addition or deletion of tests, making it a dynamic battery which reflects primarily B-cell function. It includes tests for total lymphocytes and neutrophils, sedimentation rate, CRP, screening tests for cryoglobulins

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LAB-50 AM (9-82 REV)
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CLINICAL IMMUNOLOGY
LEO P. CAMLEY, M. D.

IMMUNOLOGICAL SURVEY

PATIENT NAME, HOSPITAL NO.
S/A, ROOM NO., PHYSICIAN

CLINICAL DIAGNOSIS:

DATE RECEIVED:

ABS. LYMPH: _____ (1500-4000) ABS. PMN: _____ (1500-6000) ADULT ESR: _____

CRYOGLOBULIN _____ (NEG) IMMUNE COMPLEXES _____ (<16%) ASMA _____ (NEG)
CRYOFIBRINOGEN _____ (NEG) ANA _____ (NEG) APCA _____ (NEG)
RF _____ (NEG <1:160) _____ _____ (NEG)
CRP _____ (<3 MG/DL) AMA _____ (NEG)

SERUM PROTEIN ELECTROPHORESIS: (ADULT)
T. P.: _____ GM/DL (6.0-8.0)

IMMUNOELECTROPHORESIS: _____

IgG _____ MG/DL (630-1350) ADULT
IgA _____ MG/DL (70- 315) ADULT
IgM _____ MG/DL (55- 350) ADULT
IgE _____ IU/ML(<322) ADULT

C3 _____ MG/DL (83- 177) ADULT
C4 _____ MG/DL (15- 45) ADULT
C3PA _____ MG/DL (17- 42) ADULT
CH100_____ UNITS (>70)

IMPRESSION:

CLINICAL IMMUNOLOGY IMMUNOLOGICAL SURVEY DATE: _____

and cryofibrinogens and rheumatoid factor. Autoantibodies, serum protein electrophoresis and immunoelectrophoresis as well as quantitation of immunoglobulins including IgE are other components of the package. Evaluation of complement and Clq binding test for immune complexes are also part of the study. Lastly, the report is interpreted and released with a written statement.

Between the two laboratories, we perform 12,000 electrophoreograms per year. Almost every day from 1 to 3 monoclonal gammopathys are found. Immunoelectrophoretograms and immunofixation are performed on many of these. That is a lot of data and unless it is in some sort of a format, it is not very useful. LAD formats such as our Pediatric Immunologic Survey (Fig 2) incorporate skin testing (necessary for the pediatric population). The survey includes some aspects of B and T cells and neutrophils (Nitro Blue Tetrazolium test) and complement. These are crude screening measures, but yet, effective in detecting problems of the newborn and the young. We are able, with other laboratory data, to come up with an interpretative statement for this report.

Clinicians will accept the test if it helps them. As an example, serum T_4 is a very successful test because high quality decisions can be made on its result.

Developing batteries of tests for immunologic disorders is important for LAD packages. To begin a program for immunology, an understanding of the dynamics of serum proteins is helpful. The survival of proteins, that is, how long they last before being replaced and how they are removed is important for understanding immunoglobulins, immune complexes, etc. For example, IgG has a half-life of 25 days, IgA has a felf-life of 5 days. Why the difference? We now know that one mechanism is the desialinization route where enzymes in the plasma gradually remove sialic acid from proteins which are then susceptible to binding by hepatocyte receptor proteins. The second method is binding of old antigens by autoantibodies, a naturally occuring antibody against IgG called rheumatoid factor which is an IgM molecule is an autoantibody. It reacts with altered aged IgG molecules. For several other proteins (autoantigens) there are similar naturally occuring antibodies. For example, the T antigen of the red cell is associated with a naturally occuring serum IgM anti-T. If the antigen is exposed by enzymatic stripping which exposes the red cell T antigen, the natural occuring serum IgM anti-T reacts with the red cell. A hemolytic uremic syndrome may develop if the exposure of the red cell T antigen is extensive. The long and the short of it is, proteins wear out and are buried by one of several mechanism. The removal of sialic acid leads to removal by hepatocytes. Functional activation with autoantibody and complement fixation enhances ingestion by liver Kupffer's cells

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DEPARTMENT OF LABORATORY MEDICINE

CLINICAL IMMUNOLOGY
LEO P. CAMLEY, M. D.

PEDIATRIC IMMUNOLOGICAL SURVEY

PATIENT NAME, HOSPITAL NO.
S/A, ROOM NO., PHYSICIAN

CLINICAL HISTORY:

DATE RECEIVED:

ABS. LYMPH:	_____	ABS. PMN:	_____
STP:	_____ GM/DL (6.0-7.5)	IgG	_____ MG/DL
SPE:	_____	IgA	_____ MG/DL
CH100:	_____ UNITS (>70)	IgM	_____ MG/DL
NBT:	_____ (4-18%)	IgE	_____ U/ML
STIMULATED:	_____ (>20%)		

DHS:	24 HR.	48 HR.
CANDIDA	_____ MM^2	_____ MM^2
MUMPS	_____ MM^2	_____ MM^2
DERMTOPHYTON	_____ MM^2	_____ MM^2
DIPTHERIA - TETANUS	_____ MM^2	_____ MM^2

IMPRESSION:

CLINICAL IMMUNOLOGY PEDIATRIC IMMUNOLOGICAL SURVEY DATE: _____

Figure 2. The Pediatric Immunologic Survey is our second LAD package. It concentrates on protein electrophoresis, NBT test for neutrophile, quantitation of immunoglobulins and skin tests with readings at 24 and 48 hours. Each report is released with an interpretative written statement.