An Evolutionary Change in Diagnostic Virology

MAX A. CHERNESKY, Ph.D.

Director, McMaster University Regional Virology and Chlamydiology Laboratories, and Professor of Pediatrics and Pathology, St. Joseph’s Hospital, Hamilton, Ontario, Canada

Received February 15, 1989

The earliest laboratory diagnoses of viral infections were made by microscopy just after the turn of the twentieth century. Animal and egg inoculation were the methods of choice until tissue culture and serology accelerated the field of diagnostic virology during the fifties and sixties. More rapid methods, including electron microscopy, immunoassays, and nucleic acid probes, are now available and influencing laboratory decisions and patient care. This review discusses changes in science and society which have influenced diagnostic virology and how the discipline has responded to these influences.

Diagnostic virology by definition is that which goes into formulating the diagnosis of a viral disease. Both clinical and laboratory aspects are part of this discipline. Rapid diagnosis refers to a laboratory diagnosis achieved in time to enable an influence on patient management. Although discoveries contributing to diagnostic virology began to accumulate at the turn of the century, diagnosis and management of most of the major viral illnesses have been accomplished during the past 50 years. Other reviews on the more recent developments in diagnostic virology have appeared [1,2,3]. This review will attempt to present the advances as they have evolved and to show how change has influenced direction in the field. Finally, an attempt will be made at predictions for the future.

To illustrate the changes which have taken place recently in the utilization of diagnostic virology services, Table 1 presents a summary of specimens submitted to our laboratory from 1970 to 1986. Most diagnostic laboratories have experienced this type of growth in requests for viral isolation and antigen detection. Demand has been strong for rubella and hepatitis serology; however, requests for traditional analysis of paired sera have not grown because of its retrospective nature. Similarly, there has been a concomitant growth in labor intensiveness performed per specimen, because traditional technology is not replaced but supplemented.

Looking back at some of the key historical discoveries and focusing on diagnostic techniques, Table 2 shows examples of important discoveries in the laboratory diagnosis of viruses as etiological agents of human diseases. Pathologists in the early 1900s detected inclusions in human tissue under the light microscope, thus providing evidence of rabiesvirus infection. The first half of the century saw the development of animal and egg inoculation with patients’ specimens, as well as the laboratory diagnosis of polio, herpes simplex, yellow fever, influenza, and pox and Coxsackie viruses. The laboratory technique most responsible for launching the discipline of

Abbreviations: AIDS: acquired immune deficiency syndrome HIV, human immunodeficiency virus IA: immunoassay IEM: immune electron microscopy IF: immunofluorescence

Address reprint requests to: Max A. Chernesky, Ph.D., Professor of Pediatrics and Pathology, St. Joseph’s Hospital, 50 Charlton Avenue East, Hamilton, Ontario, Canada L8N 4A6

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diagnostic virology came in the late 1940s when Enders, Weller, and Robbins [4] reported the growth of poliovirus in tissue culture and its visualization under the light microscope. Throughout the fifties and sixties, many viruses were proven as etiological agents of diseases, using tissue culture or serology. From the sixties to the eighties, electron microscopy, immunoassay (IA), and nucleic acid hybridization became useful tools for the diagnosis of vesicular eruptions, hepatitis, and gastroenteritis. Most would agree that the seventies and eighties have been the golden age of IA, involving both radioactive and enzymatic labels, immunofluorescence (IF), and immune electron microscopy (IEM). Great success has been achieved in the diagnosis of viral hepatitis, rubella, respiratory, and diarrheal diseases.

Laboratory technology and the development of antiviral agents (both of which have been largely driven by industry) have moved diagnostic virology away from a public health approach to one of great relevance to patient management and treatment. In the 1980s, we no longer investigate a particular virus with a specific laboratory technique. On the contrary, we employ an armamentarium of technology to investigate groups of viruses which might contribute to the cause of disease. For example, a patient with upper or lower respiratory disease may have a nasopharyngeal swab or wash or a throat swab collected for investigation. The disease may be caused by any one of a variety of viruses, and therefore diagnosis will require the application of several methodologies, including rapid techniques such as IA or IF, as well as cell culture and hemadsorption. The appropriate use of available technology can now enable rapid and accurate diagnosis affecting patient and contact management in at least five categories, including viral hepatitis A and B, genital herpes, respiratory infection, gastroenteritis, and congenital infection.

It is interesting to look at what has changed the focus of viral diagnosis over the years. Newer technology has led to some outstanding discoveries. Kohler and Milstein’s original description of monoclonal antibody technology in 1975 [5] has led to new reagents and approaches in the diagnosis of infectious diseases [6]. Solid-phase immunoassays and development of molecular probes are moving the diagnostic field faster than ever during the 1980s [7,8]. Virus eradication, which for most diseases was never a consideration, has become a reality since the global eradication of smallpox [9]. Now other infections such as measles and polio are prime candidates for eradication [10], which results in greater diagnostic pressure on laboratories. Transplantation and immunosuppression have combined to prolong or improve the quality of life for a large number of people but, in turn, have created new problems with virus reactivation, in particular with the herpesvirus group. Rapid and accurate diagnosis has become

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**TABLE 1**
Specimens Submitted to the Regional Diagnostic Virology and Chlamydiology Laboratories, Hamilton, Ontario, Canada, 1970–1986

| Specimens         | 1970 | 1974 | 1978 | 1982 | 1986 |
|-------------------|------|------|------|------|------|
| Isolation or detection | 1,173 | 3,169 | 4,495 | 7,443 | 8,824 |
| Serology          |      |      |      |      |      |
| Rubella           | 493  | 5,676 | 7,529 | 8,060 | 8,351 |
| Hepatitis         | 233  | 3,827 | 4,852 | 6,384 | 9,641 |
| All other viruses | 400  | 1,493 | 1,439 | 3,681 | 3,517 |
| Totals            | 2,299| 14,165| 18,315| 25,568| 30,333|
### TABLE 2
Examples of Important Historical Discoveries of Viruses as Etiological Agents of Human Diseases, Using Diagnostic Techniques

| Techniques                      | Dates    | Viruses                                           |
|---------------------------------|----------|--------------------------------------------------|
| Microscopy                      | 1903     | Rabiesvirus                                      |
| Animal inoculation              | 1908     | Poliovirus                                       |
|                                 | 1920s    | Herpes simplex virus, Yellow fever virus,         |
|                                 |          | Rabiesvirus                                      |
|                                 | 1933     | Influenza viruses                                |
|                                 | 1947     | Coxsackievirus                                   |
| Eggs                            | 1930–40  | Vaccinia virus, Herpes simplex virus              |
|                                 | 1935     | Influenza viruses                                |
| Tissue culture or serology      | 1949     | Polioviruses                                     |
|                                 | 1950s    | Echoviruses, Adenoviruses, Parainfluenza viruses, |
|                                 |          | Reoviruses, Rhinoviruses, Cytomegalovirus        |
|                                 | 1960s    | Rubellavirus                                     |
|                                 |          | Coronavirus                                       |
|                                 |          | Lassa fever virus                                |
|                                 | 1980s    | Retroviruses                                     |
| Electronmicroscopy or immunoassay| 1960s   | Varicella-zoster virus, Hepatitis B virus,        |
|                                 |          | Hepatitis A virus, Rotavirus, Norwalk virus,      |
|                                 |          | Calicivirus, Picornavirus, Astrovirus, Adenovirus,|
|                                 |          | Human parvovirus                                 |
| Nucleic acid probes             | 1980s    | Adenovirus, Human parvovirus                     |

imperative as differentiation of organ rejection from viral tissue invasion necessitates answers from the laboratory. Newer vaccines, some genetically engineered, have also contributed to some shift in the focus of diagnostic virology. For examples, the acceptance of hepatitis B vaccination by health care deliverers has led to increased testing for immunity. Although the acquired immune deficiency syndrome (AIDS) had probably been heterosexually endemic in Central Africa for some time, the general acceptance of homosexuality as a way of life in the U.S. during the 1970s may have contributed to the spread and subsequent discovery of the human immunodeficiency
virus (HIV) in 1982. Subsequently, the large number of patients with AIDS is exerting tremendous pressure on laboratories not only for HIV diagnosis, but for diagnosis of all of the AIDS-associated opportunistic infections.

As our understanding of disease processes has increased, the management of patients with viral infections has evolved. Similarly, rapid viral diagnosis is evolving. There are now three Rapid Viral Diagnosis Groups (in Europe, Asia, and America) focusing on the development and application of technology as it relates to the clinical management and treatment of viral diseases. An expression of the speed at which research data is generated may be observed in the scientific literature. Not only have we seen growth in the number of papers published per particular virus [1], but also in the tremendous proliferation of journals focusing on viral diagnosis. Before 1970, there was little more to turn to than the Journal of Virology and the Journal of General Virology. Now we have an additional 12 journals replete with new information.

What about the future? More rapid and accurate technology can be anticipated, with particular emphasis on polymerase chain reaction enhancement of viral nucleic acid detection [11]. New and more effective treatment, more commercial kits, and better quality control as well as office and home testing can be expected. These changes in turn will set new courses and directions in the laboratory diagnosis of viral infections.

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