

Progress in Clinical Virology—1960 to 1980: A Recollection of Twenty Years

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The field of clinical virology has changed dramatically over the past two to three decades. The breakthrough achieved in the early 1950s by Enders et al. [1], namely that poliovirus can be propagated in cultured cells, proved to be of enormous significance not only in the impact made on the control of poliomyelitis, but even more importantly upon the entire field of virology. The use of tissue culture techniques has provided the foundation upon which virologists have been and are still dependent for most basic and diagnostic studies.

It was in July 1960, at the recommendation of Dr. R.H. Green, that I was appointed director of the Diagnostic Virology Laboratory at Yale-New Haven Hospital by the late Dr. J.R. Paul. The laboratory, which had been founded several years earlier, had as its major function the diagnosis of diseases of patients suspected of suffering from virus infections. At that time, I was pursuing basic studies of enterovirus replication, while the research interests of laboratory staff members were in poliomyelitis [2]. As a result, most of the techniques and facilities available for diagnostic purposes were oriented toward the isolation and identification of polioviruses and other enteroviruses. Fortunately, I started my duties during the summer months, the enterovirus season in New Haven, and most of the viruses isolated were familiar to all of us. But as summer ended and fall and winter began, influenza, parainfluenza, respiratory syncytial virus, and many others appeared on the scene. Thus, the task of learning and devising additional techniques capable of increasing the rate of virus isolation became more pressing, if only to fulfill the daily demands of the clinical laboratory. It soon became apparent that knowledge of, and experience with, methods for the recognition and characterization of the individual virus groups were confined primarily to research laboratories. Consequently, the idea of a post-doctorate course in "Diagnostic Virology" was conceived and the first session was offered in 1962 at the Yale Medical School. A manual was needed for students in the course, and the first edition of *Diagnostic Virology*, a laboratory guide, was published in 1964 [3]. In the meantime, the course was being offered on a regular basis, annually at first, then biennially. It consisted of lectures on the clinical and laboratory aspects of the common viral diseases, combined with an in-depth laboratory workshop that incorporated a series of newly developed techniques for the diagnosis of virus infections and for basic studies of viral replication.

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CHANGING INTEREST IN VIRUS GROUPS

Poliomyelitis and Influenza

It became evident that the development of new techniques for the study of a particular virus group has greatly influenced the growth of interest in that virus category. The waves of interest and surges of research activity for each virus group are represented by the number of publications reported in *Index Medicus* (Fig. 1). For example, because of the successful use of live poliovirus vaccine in the early 1960s in reducing the incidence of poliomyelitis, the interest in studying polioviruses has gradually declined. On the other hand, influenza virus infections occur annually in sporadic or epidemic form and create constant public concern, so the stable level of interest in this virus group over the years is understandable. The threat of a possible pandemic of swine influenza in 1975-76 [4] probably accounts for the increase in the number of articles published in that year and the years following.

Viral Hepatitis

Although viral hepatitis was recognized as an important clinical entity long before the early 1960s, the number of articles published was limited. Despite the tireless search for the etiology of viral hepatitis, a breakthrough did not occur until the discovery in the early 1960s of the Australia antigen, later called hepatitis B surface antigen, in the serum of hepatitis patients [5]. Subsequently, the recognition of Dane particles (hepatitis B virions) in patients' sera [6] and the application of solid-phase radioimmunoassay methods for screening hepatitis B virus antigens and antibodies [7,8] were further developments for the study of hepatitis B virus. Excretion of hepatitis A virus in the stools of patients during the acute phase of illness was known for years but the identification of hepatitis A virus particles was not possible until the use of immune electron microscopy in the early 1970s [9]. The use of these newer

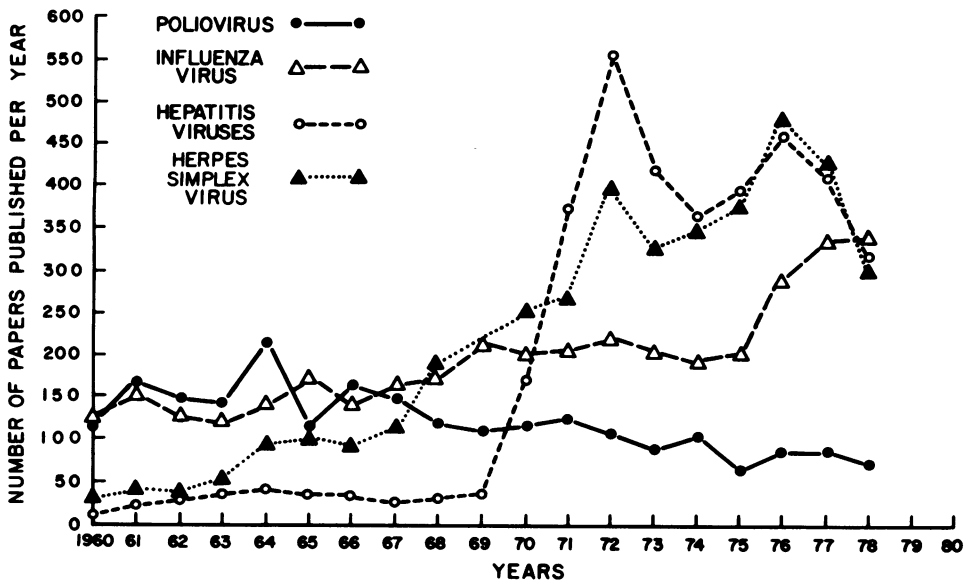


FIG. 1. Number of publications on four representative virus groups reported annually in the *Index Medicus* for 1960-1978. The variations are thought to be indicative of changing interest in different virus groups.

techniques has also led more recently to the recognition of non-A, non-B hepatitis [10]. These advances are particularly important both from a clinical and from an epidemiological viewpoint and are reflected in a sudden increase in the number of papers published during the early 1970s (Fig. 1). For further discussion of hepatitis viruses, the reader is referred to Dienstag's review in this issue [11].

Herpesvirus Group

Very few studies of herpesviruses, including herpes simplex virus, were published in the early 1960s—perhaps because they were not considered to be important clinical entities other than the occasional cases of herpes encephalitis that had been recorded. However, reports of an epidemiological association between herpes simplex virus type 2 and cervical cancer [12,13], and of a link between the Epstein-Barr herpesvirus and Burkitt's lymphoma [14], nasopharyngeal carcinoma [15], and infectious mononucleosis [16], together with the increasing rate of cytomegalovirus isolations from renal transplant recipients and varicella-zoster virus from patients treated with immunosuppressive drugs [17], led to a sudden increase in interest in the herpesvirus group, especially herpes simplex virus. This interest in the latter virus type is reflected in the large number of publications reported in the 1970s (Fig. 1). Partly because of the apparently successful treatment of herpes simplex virus encephalitis by adenine arabinoside [18], great interest in this group of viruses by clinicians and basic virologists is expected to continue for some time. The widespread circulation of herpes simplex virus in modern society, as indicated in the review by Nahmias in this issue [19], is an example showing the realization of the epidemiological impact that occurs when infection with herpes simplex virus type 2 is recognized as a major venereal disease.

RECENT ADVANCES IN TECHNOLOGY

The significance of advances in technology, especially the availability of sophisticated instrumentation on the expanding and continuing interest in virology, cannot be overemphasized. For example, studies of viral hepatitis and nonbacterial gastroenteritis, which are caused by agents that are still difficult to propagate in cell culture, can be studied by other means. Virologists are no longer dependent on laboratory animals and/or tissue culture, but may use alternative methods of viral diagnosis such as electron microscopy and immunoelectron microscopy (for further discussion see reviews by Hsiung et al. [20], Almeida [21], and Doane [22]), radioimmunoassay [7,8,11], and enzyme-linked immunoabsorbent assay [23]. Furthermore, molecular virologists have been able to develop and apply their basic knowledge to analyze clinical and epidemiological problems of the various virus infections (for further discussion see several reviews in this issue [24,25,26]). It was with a view to defining, exploring, and understanding these new approaches to clinical virology that this year's lecture series was organized, structured, and, insofar as possible, incorporated into the overall content of the course.

CONCLUDING REMARKS

In looking back over the years, it is apparent that the field of clinical virology has changed significantly. In the early 1960s, with the development of a variety of cell culture systems, many new viruses were discovered and characterized. Today, with the use of newly developed techniques and facilities for detecting viral antigens, more and more viruses are being implicated as etiological agents of obscure diseases. As

chemotherapy of viral diseases becomes a reality, pressure to develop even more effective methods for rapid viral diagnosis will increase. Thus, continued efforts in the fight against viral disease will be strengthened through the development of more effective and sensitive means for detecting the presence of these agents.

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