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WHAT'S IN STORE FOR 1984?

Introduction

As indicated in John Lawrence's letter, the Infectious Diseases Newsletter will undergo a marked change in both the editorial direction and in format. I wish Dr. Paul Hoeprich well in his endeavors and will do whatever I can to assist him in giving some energy to this new direction. For this first issue of IDN in 1984 I thought I would focus on areas that I believe will be of high activity in the coming year, some of which will culminate in definitive information which will change our concept, diagnostic practices, and therapeutic activities.

New Diseases and Causes of New Disease

A number of causes have been suggested as the basis for the occurrence of acquired-immune-deficiency syndrome (AIDS). Initially, it was believed that intensive exposure to cytomagolovirus somehow influenced lymphocyte function and produced the aberrant immunologic findings in AIDS.[1] This premise has not held up and the search has continued for other possible etiologic agents.

Suggestions have been made that the immunologic aberrations may be secondary to drug use.[2] This thesis has also not been sustained.

The search for a viral cause did not end with the cytomegalovirus hypothesis. Several observers have noted unusual morphologic changes such as vesicular rosettes in lymph node lymphoid cells and a tubular reticular structure within cisterns of smooth endoplasmic reticulae of lymphocytes from patients with AIDS.[3,4] One hypothesis to explain their occurrence is viral infection of the lymphocytes.

Studies in hemophiliacs who received factor VIII therapy but not other forms of replacement suggest that a transmissible agent, possibly in the factor VIII concentrate, results in immunologic aberrations that are not unlike those seen in AIDS.[5]

Investigators have suggested a possible link between AIDS and human T-cell leukemia virus (HTLV).[6,7,8,9] This agent has been associated previously with a rare type of human cancer. A number of lines of evidence suggest HTLV as a possible etiologic agent. First, HTLV is prevalent in the Caribbean area and in Africa, the areas of occurrence of AIDS in some populations. HTLV is an agent which affects T-cells on a very selective basis. Since the primary AIDS defect appears to be in the T-lymphocytes, it is hypothesized that an agent which primarily infects these cells might be a logical candidate. HTLV also appears to spread by intimate contact, a prerequisite in the theory of AIDS transmission. One other analogy is that HTLV causes both a cancer and an immunosuppression as is true for a number of leukemia viruses in animals. HTLV is a retrovirus with RNA in its core. Transcribed viral DNA has been found in the cells of a few patients with AIDS but not in healthy homosexual male controls. Infectious HTLV particles were isolated from one patient's T-cells and from two patients who did not have evidence of viral DNA. The virus has been identified as HTLV-1, apparently the most common type among 35 or more isolates of the virus. Antibodies against HTLV have been found in a proportion of AIDS patients and very rarely among control individuals. There are some features of HTLV which do not parallel the features of AIDS giving rise to scepticism as to whether this agent is, in fact, a cause of AIDS or simply one of the many agents with which AIDS patients can become infected.

More recently a suggestion has been made that cyclosporin produced by infection with a saprophytic fungus, Thermoacus crustaceus, may be the cause of AIDS.[10] The problem with all of the postulated infectious agents is that the immunodeficiency that is part of AIDS may predispose to infection with a wide variety of opportunistic agents. As a result, one cannot be certain that isolation of an agent or identification of host response to it in anyway reflects etiology.

My guess is that 1984 will result in the discovery of the precise cause of AIDS and its mode of transmission. Then, as with the Legionella story that preceded it, we will be able to better understand the epidemiology of this disorder and the presumed lesser forms of the disease that may occur.

Lyme disease, an acute inflammatory disorder characterized by a very specific skin rash, erythema chronicum migrans, was a puzzle for some time until Steere, Benach and others discovered a spriochete both in patients and in the Ixodes sp ticks which are the vectors.[11,12] The spriochete is unique and evokes an antibody response which can be measured as both specific IgM and IgG. In 1984 we can expect further definition of infection with this agent, including, perhaps, milder forms of the disease and even asymptomatic infections.

One of the most exciting findings reported in 1983 is the identification of plemorphic, gram negative bacteria in the vast majority of 39 lymph node specimens

from patients with cat scratch disease[13]. The cause of this disease has been extremely elusive and therefore difficult to diagnose with certainty. If the bacteria can either be isolated or otherwise identified by host response during 1984, I am certain that this will propel cat scratch disease from a medical oddity to a well characterized infection.

Will we discover new infectious diseases or the causes of some which have eluded us thus far? It is likely that the progression of infectious diseases in the past decade which are either newly identified or seem to arise de novo will continue. Obviously, I cannot predict when and where or what the nature will be, but I think physicians should be alerted to the possibility that the odd patient that they are seeing who does not conform to any textbook description may be the herald case of some new disorder. Further, a cause for disorders such as Kawaski Disease may be discovered this year.

Pathogenesis of Disease

One of the most intriguing findings in the past several decades has been the discovery of a genetic basis for immune responsiveness and, by inference, to susceptibility to infectious diseases.[14,15,16,17] Work with carefully bred animals led to the segregation of specific factors that determine genetic responsiveness and genetic susceptibility. This information has been partially translated into human experience by the association of certain white cell types, which are the reflection of these genetic characteristics, with specific inflammatory disorders. Further, ability to respond immunologically to certain antigens appears to be related at least in part to the genetic make-up of individuals in relation to certain gene loci. In 1984 I look forward to further definition of this relationship which may help to answer the several puzzling questions that confront clinicians, such as why does this child develop encephalitis with Epstein-Barr virus and this one not, or why does this child die with an overwhelming bacteremia whereas the majority of individuals do not, or why does poliovirus produce paralysis in certain individuals whereas the vast majority of exposed and infected individuals either have asymptomatic infection or nonparalytic illness? Questions such as these have plagued us and we have vaguely related them to the patient's "constitution" or to his "germ plasm". I believe we are at the threshold of discovering what that characteristic is at a molecular level.

The pathogenesis of cancer appears to be an exteremly complex matter but the discovery of oncogenes and their interrelationship with environmental influences offers the hope that we may understand the complex interactions between infection with specific agents, immunologic response to these agents, immunosuppression, and malignant transformation.[18]

Newer Diagnostic Techniques

Among the many challenges confronting a clinician who deals with infectious diseases is the segregation of individuals infected with atypical mycobacteria from all other causes of skin, lymph node and pulmonary infection. Some years ago we had available skin test material which we thought was specific enough to help us sort out individuals infected with atypical mycobacteria from those who had infection or past experience with Mycobacterium tuberculosis. These materials were removed from our use because of questions of specificity and have not yet returned to general use. It is my belief that in 1984 we will have better diagnostic methods in this area, possibly with release of skin test antigens which may have greaater specificity than those we used in the past.

One other "breakthrough" that can be anticipated with reasonable expectation is the development of rapid serologic diagnostic tests for sorting out the many viruses which produce gastrointestinal infections. Rotaviruses have proved the pathfinder in this regard, first being detected solely by their morphologic appearance in electronmicroscopy of stool specimens. This test rapidly yielded to RIA and ELISA identification which is now readily available in many diagnostic laboratories. I suspect we will not only continue to refine the diagnostic tests for rotavirus infection but can anticipate that other agents such as the parvoviruses, coronavirus and cthers masy yield to similar techniques.

The development of enzyme-linked immunosorbent assays (ELISA) promises to greatly alter our diagnostic methods.[19] Capable of being adapted to measure either antigen or antibody response, this technique offers the routine microbiologic laboratory the opportunity of a fairly specific, highly sensitive test for routine detection of a wide variety of antigens. In many ways this has obviated the necessity for some routine microbiologic procedures and has replaced more cumbersome ones in the detection of very small amounts of antigen or antibody. The adaptation of this test to an increasing number of infectious agents offers the

promise that 1984 may find routine laboratories equipped to make diagnoses more rapidly and with greater precision and sensitivity than ever before.

We can anticipate wider use of the latex fixation test for the identification of bacterial antigens[20]. This test has proved extremely useful in the detection of Haemophilus influenzae antigen and is so simple to perform that it does not require elaborate set-ups (such as is necessary with counter-immunoelectrophoresis) nor does it require elaborate skills on the part of the technical staff. It is likely that the test may be adapted to other antigens that we commonly seek.

Therapeutic Anticipation

We will continue to see third generation cephalosporins entering the United States market. Our task will be not so much to learn how to use them, but to learn which ones should not be used.[21] It is clear from our early experience with moxalactam that these drugs seldom substitute for more standard forms of therapy but do have a place in resistant infections and in certan clinical circumstances. In 1984 we will see the advent of up to 15 new 3rd generation cephalosporins, with heavy promotion and a plethora of clinical studies.

We can look forward to the completion and publication of the third cooperative neonatal meningitis therapeutic study headed by George McCracken.[21] I can anticipate that it will demonstrate that the combination of ampicillin and moxalactam is as good as, but no better than, the combination of ampicillin and amikacin. One can only hope that Dr. McCracken and colleagues will be innovative by doing a fourth clinical trial in an attempt to find a therapeutic formula which reduces morbidity and mortality from that of the current regimens.

One of the more exciting aspects of therapeutic research is the development of newer antiviral agents. For years practitioners have been plagued with the increasing recognition of the viral cause of a variety of diseases and improved methods of diagnosis including rapid identification of many viruses that is not possible with the inability to significantly influence the course, morbidity or mortality associated with these infections. Of course the difficulty has been that effective antiviral treatment usually involves interference with viral replication which closely parallels physiologic processes of the normal cell. As a result toxicity has been a severely limiting factor even if the agent was therapeutically effective. A few agents have survived this dilemma and have become useful in clinical practice; the most recent being acyclovir for herpes virus infection.[22] Of great promise is that topical and oral forms of this antiviral agent may find a niche in our therapeutic armamentarium. One of the most exciting findings as 1983 came to a close was the report that ribvarin was successful in the treatment of respiratory syncytial-virus infections.[23] These promising preliminary findings suggest we can look forward to newer and useful antivirals in 1984.

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