EDITORIAL

The EB Herpes-like Virus: Etiologic Agent of Infectious Mononucleosis?

The recent announcement by the Doctors Henle of Philadelphia of the finding of an antibody against the EB virus in the sera of all cases of infectious mononucleosis (IM) studied was the source of some excitement in immunologic, oncologic, and hematologic circles. In a prime example of serendipity, the Henles, who were testing various sera for antibody to this newly-discovered herpes-like virus, found that one of their technicians, previously negative, had developed a positive anti-viral antibody when she became ill with infectious mononucleosis. This led to a large scale study and eventually to the strong implication that the EB virus was the long-sought-for etiologic agent of IM.

The EB virus, a “new” member of the herpes group of viruses, had previously been cited as the probable cause of the Burkitt lymphoma. It was first found by electron microscopy in cells of Burkitt lymphoblasts, and its presence was confirmed in various cell strains in tissue cultures from cases of that disease. Epstein and Barr (EB) and their collaborators prepared viruses from bulk cultures of their EB 3 strain of Burkitt lymphoma lymphoblasts and then, using purified viral cultures, were able to produce an antibody specific for the EB virus by immunization of rabbits. With the use of an immunofluorescent technic, the anti-serum gave a “brilliant apple-green fluorescence” with cells of EB 3 Burkitt lymphoblast cultures, but not against normal human lymphocytes, nor against cells infected with other viruses, including those of other herpetic viruses.

Search for a viral agent in the Burkitt lymphoma has been pursued vigorously, especially since epidemiologic studies indicated the possibility of an insect vector for an infectious agent. In addition to the EB virus, at least two other viruses have been implicated in the disease including that of herpes simplex (Sarah Stewart) and reo virus 3 (Stanley). No direct evidence that any one of these agents is the causative agent of the Burkitt lymphoma has thus far been obtained.

In IM, the strong presumption that a virus is the cause of the disease has been held for a number of years, especially since no other type of infectious agent has been demonstrated. Much inferential data are present to indicate that the disease might be transmitted through rather vigorous osculatory maneuvers, perhaps more prevalent in adolescents and young adults than in children or older people. Although attempts to induce the disease in volunteers and monkeys by injections of blood, saliva, and other secretions have been largely unsuccessful, they have not ruled out a viral agent. Does then the recent work of the Henles indicate that the EB virus is etiologic in IM?

It should first be stated that the Henles did not, in their first studies, find
a virus but rather an antibody against the EB virus as detected by immunofluorescent technics using the patient's serum for source of antibody. This work was recently confirmed by Gerber et al.\textsuperscript{11} who found complement-fixing antibodies to herpes-like virus in 21 consecutive cases of IM. These antibodies were absent in all sera before the patients became ill, were distinct from heterophile antibodies and persisted for lengthy periods. It was concluded that the development of complement-fixing antibodies to this herpes-like virus (originally derived from a Burkitt lymphoma) was closely associated with IM. The Henles found that the antibody was present in about 20 per cent of young children\textsuperscript{1} although the occurrence of IM in young children is distinctly unusual. Antibodies against EB virus were furthermore found in the sera of some patients with leukemia, and in about 90 per cent of the sera obtained from normal American adults.\textsuperscript{12} In more direct studies reported recently, both the Henles\textsuperscript{13} and Moses et al.\textsuperscript{14} found electron microscopic evidence of herpes-like virus in IM cell lines in continuous tissue culture.

IM is invariably associated with the presence of many abnormal antibodies, including 19S cryoglobulins, positive serologic tests (for syphilis), heterophile agglutinins, cold hemagglutinins, isoantibodies, and at times, even autoantibodies. In this welter of antibodies, another antibody reacting against EB virus need not indicate that the virus is etiologic or even that the antibody is directed against a specific virus. The presence of heterophile antibodies against cow and sheep red cells in IM does not indicate that the antigens are derived from cows or sheep; possibly the distorted lymphocytes of IM might produce antibodies which are also "distorted" or abnormal, thus reacting against normal antigenic components. On the other hand, antibody to herpes-like virus appears to be quite distinct from the other antibodies of IM and has been shown (from sera stored at Yale University School of Medicine) to persist for many years.\textsuperscript{11}

Thus, although the antibody against EB virus is "associated" with IM and may indeed be specific for that virus, these features of themselves do not prove that EB virus is the etiologic agent of the disease. Herpetic viruses are often found in association with lymphoproliferative disorders; however, their etiologic relationship to the disease has by no means been clarified. For example, in chronic lymphocytic leukemia, herpetic infections are very common, notably those of the simplex and zoster types. These are usually seen in the latter phases of the disease and may result in severe and at times life-threatening situations.\textsuperscript{15} Little if any thought has been given to linking the viruses of these diseases etiologically to the chronic leukemias. Rather, it has been assumed that the viruses are latent, long-term residents which might become active under certain circumstances, thus resulting in various types of herpetic disease.\textsuperscript{16} The circumstances bringing a latent or resident virus to the fore are obscure. It is conceivable that herpetic viruses might be closely associated with or have a special affinity for lymphocytes and might thus become increased or more obvious either during an increase in lymphocyte mass or in response to ionizing radiation, chemical and drug exposure or other viral infections. In these various situations, the development of a temporary immuno-
deficient state may be an important factor in the development of an active infection by a resident virus. It should also be noted that at least two observers have previously reported a rise in titer of antibodies to certain viruses in IM.\textsuperscript{17}

What has been said thus far does not by any means rule out the possibility that the EB virus is the true etiologic agent of IM; in fact, it may well be. However, it is now rather generally agreed that more evidence is needed, including more animal (and perhaps even human) experimentation before final acceptance can be made. In any event, all these new and exciting findings in IM do not lessen one's enthusiasm for this "fascinating disease," which is certainly worthy of much further study, not only from the etiologic standpoint, but as a form of self-limited leukemia and a bizarre immunoproliferative reaction.\textsuperscript{18} Perhaps there is a close relationship of mononucleosis to the Burkitt lymphoma, which unlike most cases of lymphosarcoma responds so readily to certain chemical agents. The present studies of the Henles and others reported here indicate how difficult it is, even in these sophisticated days of virologic methodology, to pinpoint with any degree of accuracy the exact relationships of virus, viral antibody, or any other indications of virus to such human diseases as leukemia, the Burkitt lymphoma, or infectious mononucleosis. One has the impression that progress in interpreting these possible relationships is temporarily bogged down for want of a unifying thread. Hopefully, this will soon emerge.

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REFERENCES


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