

Current Developments in Virology _____

Scientists from around the world met at WHO Headquarters in Geneva not long ago to review current knowledge on the viral diseases and to draw up a program for the next decade aimed at dealing with the public health problems that these diseases cause. It was determined that attention should be given first to working out public health procedures for those diseases which affect large segments of the population and for which immunization is practical. The next priority was assigned to diseases that have implications for international health but for which vaccines are not yet available. A third order of priority was established for diseases that still require much basic research and whose continued study is urged. The *Bulletin* is publishing selections from this meeting's short working papers in three installments. Those dealing with the first two priority areas were published in numbers 3 and 4 of 1976. The four selections presented here deal with the third area—diseases requiring considerable further study.

THE HERPESVIRUS GROUP¹

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Several agents in the herpesvirus group are known to infect man. They cause a wide variety of conditions, ranging from coldsores to chickenpox and shingles. At the same time a number of the herpesviruses have been linked with malignant diseases in both lower animals and man.

At least 25 viruses have been placed in the herpesvirus group on the basis of their DNA genome and common architecture. Within the group, herpes simplex virus types 1 and 2, varicella-zoster virus,

Epstein-Barr (EB) virus, and cytomegalovirus infect man. Types 1 and 2 virus are readily found extracellularly in the fluid phase of tissue cultures, but the other members of the group are more firmly associated with the cell. Although varicella and zoster strains have been grown in a number of tissue cultures, they have not yet regularly been obtained free in the fluid phase (except when grown in cells from human thyroid tissues). The EB

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herpesvirus appears to replicate only in human lymphoid cell cultures.

After inactivation with ultraviolet irradiation, herpesvirus types 1 and 2 can still cause oncogenic transformation of hamster cells. Functional viral genetic information is found to be present in the tumor cells.

Herpesviruses that infect lower animals are the B virus of Old World monkeys; herpesviruses saimiri, aotus, and ateles; marmoset herpesvirus of New World monkeys; pseudorabies virus of pigs; virus III of rabbits; infectious bovine rhinotracheitis virus; equine rhinopneumonitis (equine abortion) virus; canine herpesvirus; infectious laryngotracheitis virus of fowl; and cytomegaloviruses of monkeys, guinea pigs, mice, and other animal species. Herpesviruses are also known to infect cold-blooded animals (frogs and snakes). The widespread occurrence of herpesviruses in primates has previously been discussed in a paper by Barahona et al. (1).

Herpesviruses have also been linked with malignant diseases in man and lower animals: herpes simplex virus types 1 and 2, respectively, with labial and cervical carcinomas of man; EB virus with Burkitt's lymphoma of African children and with nasopharyngeal carcinoma; Lucké virus with renal adenocarcinomas of the frog; Marek's disease virus with a lymphoma of chickens; Hinze virus with a lymphoma of rabbits; and a number of New World primate herpesviruses with reticulum cell sarcomas and lymphomas in these animals.

Herpes Simplex Virus

Herpesvirus types 1 and 2 may produce various specific clinical entities, and the infections themselves may be either primary or recurrent. Primary infections which occur in persons without antibodies often result in the virus assuming a latent state in the host. Latent infections persist in persons with antibodies, and recurrent infections are common (e.g. recurrent

herpes labialis). The primary infection in most individuals is clinically inapparent and thus often not recognized. However, antibody production invariably accompanies the infection. The recurrent attacks often follow nonspecific stimuli such as exposure to excessive sunlight, fever accompanying certain infections, menstruation, or emotional stress.

Herpesvirus type 1. The clinical entities attributable to herpesvirus type 1 include the following: acute herpetic gingivostomatitis (aphthous stomatitis, Vincent's stomatitis), eczema herpeticum (Kaposi's varicelliform eruption), keratoconjunctivitis, meningoencephalitis, herpes simplex (herpes febrilis, herpes labialis).

Herpesvirus type 2. The clinical entities associated with herpesvirus type 2 include genital herpes (herpes progeneralis) and neonatal herpes.

Miscellaneous. Localized lesions of the skin caused by types 1 or 2 may occur in abrasions which become contaminated with the virus (traumatic herpes). Mild aseptic meningitis has been attributed to the virus, and recurrent episodes of meningeal irritation have also been observed. In most geographic areas patients with cervical cancer have a high frequency of type 2 antibodies.

Herpesviruses are susceptible to photoinactivation when presensitized with substances such as neutral red or proflavine. Application of these agents to active type 1 and type 2 skin lesions, followed by adequate exposure to light of the proper wavelength and of sufficient intensity, reduces the duration of the lesions and the rate of recurrence.

Varicella-Zoster Virus

Varicella (chickenpox) is a mild but highly infectious disease, chiefly of children, characterized by a vesicular eruption of the skin and mucous membranes. In im-

munocompromised children it can be severe.

Zoster (shingles) is a sporadic incapacitating disease of adults (rare in children) which is characterized by an inflammatory reaction of the posterior nerve roots and ganglia; it is accompanied by crops of vesicles (like those of varicella) over the skin served by the affected sensory nerves.

The varicella and zoster viruses are identical agents, the two diseases being the result of different host responses. Previous infection with varicella leaves the patient with enduring immunity thereto, whereas zoster may occur in persons who have contracted varicella at an earlier date. The latter probably represents reactivation of a varicella virus infection which has been latent for many years.

Individuals with a recent history of varicella or zoster infection respond to a herpes simplex infection with a concomitant rise in complement-fixing antibody to both herpes simplex and varicella-zoster viruses.

A rapid way of differentiating between vesicular lesions caused by herpesviruses (lesions due to herpes simplex or varicella-zoster viruses) and those caused by poxviruses (smallpox or generalized vaccinia) is to examine negatively stained vesicle fluid with the electron microscope to detect the presence of typical herpes or poxvirus particles.

Gamma globulin with a high specific antibody titer prepared from the pooled plasma of patients convalescing from herpes zoster (zoster immune globulin) can be used to prevent or modify the development of illness in immunocompromised children who have been exposed to varicella. Standard immune serum globulin is without value because of its relatively low titer of varicella antibodies.

Cytomegalovirus

Cytomegalic inclusion disease is a generalized infection of infants resulting from

intrauterine or early postnatal infection with cytomegalovirus. (Indigenous cytomegaloviruses exist in several animal species). The disease is characterized by large basophilic (or sometimes eosinophilic) intranuclear inclusions in the salivary glands, lungs, liver, pancreas, kidneys, endocrine glands, and occasionally in the brain. Most fatalities occur in children under two years of age. Inapparent infection is common during childhood and adolescence.

Congenital cytomegalic inclusion disease was once believed fatal in all cases, but in fact infants with the disease may survive initial infection and live for many years. A significant proportion of unexplained microcephaly and mental retardation may be caused by congenital cytomegalovirus infections.

Patients with malignancies or immunologic defects or those undergoing immunosuppressive therapy for organ transplantation may develop cytomegalovirus pneumonitis, hepatitis, and occasionally generalized disease; the relative importance of primary infection versus reactivation of a latent infection in such cases remains to be clarified.

Except in the case of congenital infection, the mechanism of virus transmission is still unknown. Widespread infection with cytomegalovirus does occur, as indicated by an increase in the rate of antibody appearance with age (reaching 80 per cent in individuals over 35). In addition, the rate of virus excretion among institutionalized children is 10 times that among children of comparable age in the population at large, suggesting that the virus is transmitted by close contact.

Epstein-Barr Herpesvirus

EB virus, an antigenically distinct member of the herpes group, is believed to be the etiologic agent of infectious mononucleosis. It has also been associated with nasopharyngeal carcinoma and with Bur-

kitt's lymphoma, a tumor of children (mostly boys) indigenous to Central Africa. The presence of EB virus was initially detected by electron microscopy in a small proportion of cells in continuous lymphoblastoid cell lines derived from a Burkitt's lymphoma. EB virus has also been detected in lymphoblastoid cell lines derived from nasopharyngeal carcinomas and peripheral blood leukocytes of patients with infectious mononucleosis, as well as in lines derived from normal individuals.

Seroepidemiologic studies using the immunofluorescence technique and the complement-fixation reaction indicate that infection with EB virus is common in different parts of the world and that it occurs early in life. In some areas, including the urban United States, about 50 per cent of the children one year of age, 80 to 90 per cent of the children over age four, and 90 per cent of the adults have antibody to EB virus. The mechanism of transmission is unknown.

Antibody to EB virus has also been found in nonhuman primates, and it is probable that some of these animals were infected in nature. In addition, EB virus has been detected in lymphoblastoid lines derived from peripheral leukocytes of normal chimpanzees and baboons.

Herpesvirus B

B virus infection of man is manifested as an acute ascending myelitis and encephalitis. Cases have arisen following the bites of apparently normal monkeys that were healthy carriers of the virus and also following contact with materials (tissue-culture fluids) derived from monkeys. Human cases are rare, but they have become more widespread since the number of persons handling monkeys and preparing vaccines from kidney cultures has increased. Herpesvirus B is most commonly found in rhesus, cynomolgus, and bonnet macaque monkeys.

SUMMARY

Man is infected by several agents in the herpesvirus group, including herpesvirus types 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and herpesvirus B.

Herpesvirus types 1 and 2 cause infections that may be either primary or recurrent, leading to a variety of specific clinical conditions. The primary infection is clinically inapparent in most individuals. Attacks from recurrent infections often follow nonspecific stimuli such as excessive exposure to sunlight, fever accompanying certain infections, menstruation, or emotional stress.

Varicella-zoster virus, as its name implies, can cause either chickenpox or shingles. The difference in the two diseases is due to differing host response.

Cytomegaloviruses can produce a generalized infection in infants (cytomegalic inclusion

disease) which is often fatal. Most deaths occur in children under two years of age. These viruses can also cause pneumonitis, hepatitis, and sometimes generalized disease in subjects with malignancies, immunologic defects, or organ transplants requiring immunosuppressive therapy. A significant proportion of unexplained microcephaly and mental retardation may be caused by congenital cytomegalovirus infections.

Epstein-Barr virus appears to be the etiologic agent of infectious mononucleosis. It has also been associated with Burkitt's lymphoma, a tumor of children (mostly boys) indigenous to central Africa.

Herpesvirus B causes an acute ascending myelitis and encephalitis, resulting occasionally from the bites of apparently healthy monkeys or from tissue-culture fluids derived from monkeys.

REFERENCE

- (1) Barahona, H., L. V. Meléndez, and J. L. Melnick. A compendium of herpesviruses isolated from nonhuman primates. *Intervirology* 3(3):175-192, 1974.