SUMMARY

Two "new" virus infections, Marburg and Lassa fever, now constitute diseases of public health importance in several countries of Africa, especially West Africa. Lassa fever has an insidious onset, is initially difficult to diagnose, has "nonspecific" clinical symptoms which have been confused with yellow fever and typhoid, shows evidence of persistent infection, is tremendously contagious, has a high mortality rate, and in particular exhibits unusual nosocomial propensity. It has also been shown to be the cause of premature births and spontaneous abortions in pregnant women. The virus is transmitted by the respiratory route and by direct contact with contaminated materials. Persistent complement-fixing antibodies have been demonstrated in patients recovered from the disease. The causative agent, a member of the arenavirus group, is known to be enzootic in rodents, especially *Mastomys natalensis*.

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ENTEROVIRUSES OTHER THAN POLIOVIRUS[1]

Reisaku Kono[2]

Research is underway to elucidate the role of enteroviruses in certain specific conditions—cardiac disease, nephritis, diabetes, hemorrhagic conjunctivitis. Heart disease has been definitely linked to five types of Coxsackievirus B; also, two types of Coxsackievirus A, along with two echoviruses, are strongly suspected.

There are now 71 known types of enteroviruses, including poliovirus types 1, 2, and 3. The apparent role of enteroviruses in certain specific disorders will be discussed.

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[2]Director, Central Virus Diagnostic Laboratory, National Institute of Health, Tokyo, Japan.

Cardiac Diseases

According to the WHO yearly virus report, 1,295 cases of viral cardiac disease were reported in the five-year period 1969-1973. In 300 of these cases (23.3 per cent), the most prevalent agent was Coxsackievirus B (CBV). These data, together with other published reports, provide good justification for believing that CBV plays a central

role in the causation of viral cardiac disease (involving 20 to 30 per cent of the cases). Coxsackievirus B-5 (CB5) has been found most frequently, with CB3, CB2, CB4, and CB1 following in that order; CB6 has rarely been encountered. According to the literature, however, CB3 and CB4 seem to play a more important role in cardiac disease than in other pathologic conditions.

Along with rubella virus, CBV has been suspected to be a cause of congenital heart disease. It has been quite distinctly documented that neonatal CBV infection causes encephalomyocarditis syndrome, which is often fatal (*1*), and evidence has also accumulated with regard to the role of CBV in idiopathic myocardiopathy in older children and adults who have never had a history of acute rheumatic fever (*2*).

Coxsackievirus A (types 4 and 16) and echovirus (types 9 and 22) might also be associated with some forms of viral heart disease (*3*), but there is little information on the exact picture or on the clinical importance of these viruses.

It has been reported that damage to the heart in acute CBV infection gives rise to chronic myocardiopathy, chronic constrictive pericarditis, and possibly endocarditis (valvulitis). An immunologic process, especially when mediated by T-cell function, has been suggested by animal experiments for the development of continuing myocardial damage (*4*).

Nephritis, Pancreatitis, and Diabetes

Burch et al., using immunofluorescence, found CB4 antigen and globulin in the glomeruli of experimentally infected mice for as long as six to eight weeks, as well as in some human kidney removed at necropsy. They suggested the possible etiologic role of CBV and other enteroviruses in glomerulonephritis (*5*).

Since there have been case reports of CB3 and CB4 infections in the pancreas of human infants, and since pancreatitis is a common finding in CBV-infected mice, it has been suspected that CBV might be related to the etiology of human diabetes. Indeed, CB4 was incriminated in the development of juvenile diabetes in a seroepidemiologic study by Gamble et al. (*6*), although such seroepidemiologic studies (*7*), as well as experimental reproduction of diabetes with CBV (*8, 9*), have been controversial. On the other hand, several workers have confirmed that encephalomyocarditis virus can cause diabetes in male DBA/2N mice (*10, 11*). These data are of interest and are worthy of further study.

Hemorrhagic Conjunctivitis

Enterovirus 70 (EV70) has been identified as a causative agent of a new syndrome, acute hemorrhagic conjunctivitis (*12, 13*). The disease first broke out in Ghana in 1969; as of 1971 it had spread to other African and some European countries (*14*). Another epidemic focus emerged in Java in 1970; the disease then swept all over Asia the following year and reached some parts of Oceania in 1972. Since that time it has settled in these epidemic areas, appearing repeatedly in the summer months. North and South America have not yet been affected.

The syndrome's most prominent clinical feature is subconjunctival hemorrhage; the prognosis is usually benign, except for the rare neurologic complications which are described below. Male preponderance has been observed in most outbreaks; young adults (20-30 years of age) show the highest morbidity rate. However, the rate of positive antibody response to EV70 is highest in children; hence subclinical infection may be common in younger age groups (*14*).

EV70 has been isolated in Japan, China, Hong Kong, Singapore, Indonesia, Thailand, Morocco, Tunisia, Zaire, and several European countries. But the earliest isolates from Singapore (1970) differed from EV70

and were identified as a variant of CA24 virus (*15*). Since then the similar agent was recovered from epidemic conjunctivitis in Southeast Asia alternatively or concurrently with EV70 (*16*). It is thus apparent that the worldwide pandemic has been caused by a single antigenic type of EV70, but a variant of CA24 has been responsible for some outbreaks of conjunctivitis in Southeast Asia.

EV70 shares the general properties of enteroviruses, but it has seldom been isolated from feces and, hence, is not considered enterotropic. Most strains grow best at 33°C; 39°C is too high a temperature for them. This characteristic may explain enterovirus 70's predilection for the relatively cool conjunctival mucous membrane (*17*). Some wild strains, however, can grow at 39°C and tend to cluster in particular epidemic areas. Such strains resemble attenuated poliovirus (Lsc 2ab) and are unlike wild poliovirus with regard to sensitivity to cultivation temperature.

Along with the experimentally proved neurovirulence of EV70 in primates (*18*), human neurologic complications such as radiculomyelitis and cranial nerve involvement have been observed in India (*19*), Taiwan (*20*), Senegal (*21*), and Thailand (*22*). Motor paralysis is the most striking feature during the whole clinical course, and some patients experience residual paralysis and muscle atrophy as major neurologic sequelae. Unlike poliomyelitis, this condition occurs mainly in adults and is more prone to attack males. Although motor paralysis has been known to occur sporadically in infections with various enteroviruses other than polio, EV70 is considered unique because of its ubiquitous neurovirulence, even though this is not strong. Consequently, the future trend of neurovirulence must be carefully watched with this virus.

Recommendations

- The etiologic role of enteroviruses, especially CBV, in cardiac disease, nephritis, pancreatitis, and diabetes should be studied and their impact on public health assessed.
- Investigations should be undertaken to find out whether these enterovirus infections result in chronic human disease such as chronic cardiomyopathy, chronic nephritis, and diabetes—and if so, what the pathogenesis is.
- In view of a new pandemic of hemorrhagic conjunctivitis, vigilance is necessary to detect the emergence of new enteroviruses. In this connection, epidemiologic studies of hemorrhagic conjunctivitis should be continued.
- The trend of enterovirus 70 neurovirulence must be carefully watched in the future.

SUMMARY

The role of enteroviruses in certain specific disease—cardiac disease, nephritis, diabetes, and hemorrhagic conjunctivitis—is examined. It has now been well documented that Coxsackievirus B (types CB1 through CB5 but not CB6) is the main pathogen involved in various clinical forms of viral heart disease. Coxsackievirus A (CA4 and CA16) and echovirus (types 9 and 22) may also be associated with viral heart disease.

In regard to the etiologic role of enteroviruses in nephritis, pancreatitis, and diabetes, again CBV, especially CB3 and CB4, has been suspected, but the data are controversial and further studies are needed.

Hemorrhagic conjunctivitis, a newly observed clinical entity, is caused by enterovirus 70. It has spread to four continents (not including the Americas) in a pandemic fashion since 1969 and is now one of the common eye infections in these areas. The virus has some neurovirulence, and motor paralysis is known to occur as a complication; hence it should be carefully watched in the future.

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