SYMPOSIUM ON WORLD MEDICINE

Arthropod-Borne Viral Encephalitis

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THE VIRUSES causing the arthropod-borne encephalitides and other related disease syndromes form a group that might be considered the epidemiologist's dream. Epidemiologic studies of this group require the teamwork and knowledge of the epidemiologist, agriculturalist, sanitary engineer, ornithologist, mammologist, veterinarian, virologist, immunologist, and clinician.

In keeping with the theme of this symposium I will emphasize the worldwide aspects of the encephalitides. The scope will be broad rather than specific. I will discuss in general the range of clinical syndromes, the spectrum of vectors, the spectrum of epidemiologic patterns, determinants of geographic distribution patterns, currently recognized world distribution, the number of different viruses, and, briefly, prevention and control.

The term "arthropod-borne viral encephalitis" was introduced by Dr. William C. Reeves and myself many years ago to replace what we considered less suitable terms such as epidemic encephalitis, summer encephalitis, and arthropod-borne encephalitis. Recently I suggested a further change since many related viruses in the group produce diseases other than encephalitis and possibly all are zoonoses, with man the occasional and accidental host in the primary biological cycle of the virus.

This new term is the arthropod-borne viral zoonoses. To shorten this, several abbreviations have been suggested, the most common being "arbor" for arthropod-borne, but I prefer "arbo" since "arbor" is a Latin word and suggests that this is a disease of trees and is caused by a plant virus.

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Range of Clinical Syndromes

The range of human clinical syndromes caused by the arbo viruses is indicated in the following list. A few named viruses are given as examples in each of three categories. Nearly all the viruses in the encephalitides group and all those in the other two groups produce encephalitis in the laboratory mouse. The second category of clinical syndromes includes fevers with and without rash and sometimes with arthralgia, and the third category is a group of hemorrhagic fevers.

1. Encephalitides (essentially all produce encephalitis in mice): eastern encephalitis (EE), western encephalitis (WE), Venezuelan encephalitis (VE), St. Louis encephalitis (SLE), Japanese B encephalitis (JBE), and Murray Valley encephalitis (MVE).
2. Fevers with and without rash: dengues, Colorado tick, West Nile, phlebotomus, Mayaro, Chikungunya, and Gulu.
3. Hemorrhagic fevers: yellow fever, Philippine, Thai, Kyasanur Forest, Omsk, Crimean, and Argentinian.

Spectrum of Vectors

The spectrum of vectors of the arthropod-borne viral zoonoses includes mosquitoes of almost all genera, hard and soft ticks, phlebotomus or sand flies, and possibly mites. Mosquitoes transmit a majority of these viruses. Some tick vectors are capable of transmitting the viruses transovarially. The tickborne group includes Russian spring-summer encephalitis (RSSE), Kyasanur Forest fever, and Colorado tick fever. Mites have been incriminated on

epidemiologic evidence in the transmission of epidemic hemorrhagic fever of the Korean or Manchurian type. For some agents, the vector is unknown, but for most of these it will probably be found to be a mosquito.

Epidemiologic Patterns

The chart summarizes the epidemiologic patterns by illustrating the cycles recognized for a number of the arbo viruses. This information has been obtained through a great deal of careful field and laboratory research. Understanding these patterns is fundamental to understanding the distribution of these agents, the seasons in which the diseases occur, and the problems of control.

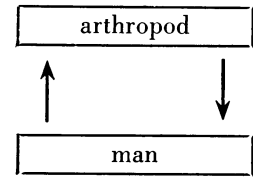
The first cycle requires viremia in the human host and an anthropophilic vector, usually a domestic one. Under these circumstances there can be transmission from man to an arthropod and then directly to other persons. This cycle is the most explosive type of disease progression among persons and leads usually to the epidemics with highest morbidity rates. Examples of these diseases are urban yellow fever, dengue, and phlebotomus fever.

The second cycle is much more complicated and may be basic to the first cycle. Many more diseases are in this latter group, which is a typical zoonosis pattern. The important vertebrate host is frequently a bird (cycle 2a), and the arthropod vector is one that feeds commonly on birds and only occasionally on man. Thus, the virus is maintained in nature, going from bird to vector to bird, but the vector occasionally bites man. If adequate viremia does not develop, man is a terminal host. If viremia does develop and there are anthropophilic domestic vectors, the first cycle described may continue. The typical members of this group, that is those in which man is an accidental or terminal host, include the well-known viruses of western encephalitis and eastern encephalitis.

Or the principal vertebrate host may be a lower mammal (cycle 2b). The result is essentially the same. Examples of this cycle are jungle yellow fever, Russian spring-summer encephalitis, Colorado tick fever, and others. In jungle yellow fever the vertebrate host is usually the monkey and the vector, a treetop mosquito,

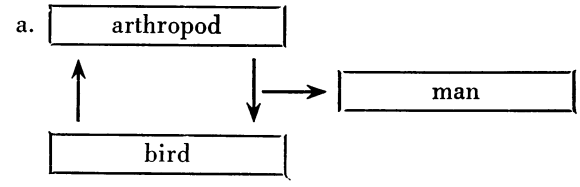
Epidemiologic patterns of arbo viruses and some of the diseases

Cycle 1: Adequate human viremia and anthropophilic vector:

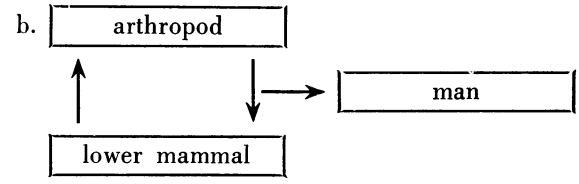


urban yellow fever, dengue, phlebotomus fever

Cycle 2: Inadequate human viremia or zoophilic vector, or both:



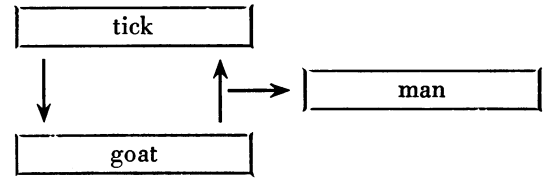
WE, EE, SLE, JBE



jungle yellow fever, RSSE, Colorado tick fever

Cycle 3: Combination of 1 and 2

Cycle 4: Milkborne:



diphasic meningo-encephalitis

while in Russian spring-summer encephalitis the vertebrate host is more frequently a rodent and the vector is a tick.

The third cycle is the complicated combination of cycles 1 and 2 and is excellently illustrated by jungle yellow fever and urban yellow fever. A man is bitten in the forest by a mosquito infected by a monkey, goes to the city at a time when he has viremia, local *Aedes aegypti* pick up the virus, and then the mosquito-to-man-to-mosquito-to-man cycle continues.

The fourth cycle, a modification of cycle 2b, is currently illustrated by only one virus. A tick infects a goat, but the virus is excreted in the goat's milk and man can be infected by drinking the milk. Explosive epidemics in man have occurred as a result of this type of transmission. The disease is called milkborne diphasic meningo-encephalitis in the U.S.S.R.

Determinants of Geographic Distribution

Means of introduction and maintenance determine the geographic distribution of the arthropod-borne viral zoonoses. A virus may be introduced where it has not existed previously by an infected man arriving in the area at a time when he develops viremia. The virus can thus be picked up by local vectors. In this fashion yellow fever and dengue, for example, have been introduced many times in years past in coastal cities of the United States. Or introduction can occur by importation of a vertebrate, other than man, with viremia, or by importation of infected arthropods by plane, boat, train, or automobile. All these events have probably served as methods of introduction of viruses in the past.

In addition to transportation by man or in his vehicles, the migration of infected birds is another distinct possibility as a means of introduction which has received much attention in recent years. A bird may be infected in an endemic area, fly for great distances during migration, and arrive in an area free from the virus, but viremia in the bird serves as a source of infection for local vectors. Another potential source, in addition to the viremic bird, is minute infected vectors carried in a bird's feathers. These vectors may transfer to local birds, thus serving as the means to implant the new virus.

After introduction of the virus there must be means for maintenance. In the first situation, there is a suitable, year-round vector present in abundance and an adequate number of susceptible, potentially viremic hosts so that the virus cycle may continue throughout the year. These requirements are met most frequently in the tropics, and under these circumstances, there is no difficulty in understanding how the virus may maintain itself. However, in temperate zones where the vector or vector's activity is only seasonal, although there are adequate numbers of potentially viremic hosts in the area, some special mechanism must exist for carrying the virus through the winter season when the vectors are not normally active and biting.

A great deal of research has been devoted to seeking this mechanism for several viruses during the past 15 to 20 years without obtaining definitive answers. Western, St. Louis, and eastern encephalitis, as they occur in this country, are examples of this difficulty as is Japanese B encephalitis in the Far East. Considered and studied intensively as possibilities are hibernation of infected vectors, transovarian infection, and latent infection in birds, snakes, or other vertebrates, with viremia appearing in the spring or early summer at the time that the mosquito vectors become available. If there is no suitable method for carrying the virus through the winter in a reservoir in a particular area, the virus disappears until it is reintroduced during the vector season by one of the means described previously. In addition to the viruses already mentioned, dengue and yellow fever may be maintained in the coastal areas of the United States by such mechanisms. It has been suggested that eastern encephalitis is being reintroduced into coastal areas of eastern United States by birds migrating from the south or by some other as yet unknown mechanism.

Currently Recognized World Distribution

I shall discuss the recognized distribution of the arbo viruses very briefly, partly because the information is changing so rapidly that current knowledge will be completely out of date within 1 or 2 years.

We can state rather clearly that these viruses are transmitted only in parts of the world where

there is a season of warmth adequate for vector development and for intrinsic incubation of the virus in the vector. These viruses will not multiply in the vector unless the temperature remains above certain levels. At the lower minimum levels, the incubation period is prolonged and, therefore, the likelihood of repeated cycles of infection is minimal. For this reason, the Arctic areas are essentially excluded from the distribution pattern.

In this hemisphere members of this group of viruses are recognized from southern Canada to the tip of South America. Viruses have been recognized from Scotland, Scandinavia, European U.S.S.R., to the southern tip of Africa. In the Far Eastern areas viruses are recognized in the maritime provinces of the U.S.S.R., Korea, and Siberia to the southern tip of India. In the Pacific, they are recognized in the Japanese islands, the Ryukyus, the Philippines, the Marianas, Indonesia, Australia, and New Zealand. In short, the world is pretty well covered except for the Arctic areas.

I do not mean to imply, however, that these viruses are evenly distributed. There are many localities where they have not been introduced or where suitable vector or vertebrate hosts are not present. Such areas are apparently entirely free from any of these agents. Therefore, the distribution of the arbo viruses is spotty and varies greatly from the distribution of such viruses as measles, influenza, and poliomyelitis which exist where there are human hosts and travel, for vectors and other vertebrate hosts are not essential in their cycle.

Number of Viruses

The number of viruses in the arthropod-borne group which are now recognized and studied adequately enough to determine that each is a distinct entity is probably near 150. The number increases almost weekly. Those known to produce disease in man are fewer; my estimate of these at the moment would be about 50.

Antibody studies, however, reveal that many more infect man, but their disease potential has not yet been determined. Because of the crossing of antibodies between certain of these viruses, it cannot be determined with certainty at present whether detected antibodies for a certain virus means infection with that virus or with another closely related to it. This is another reason why it is difficult to give an accurate number of those which infect man. Undoubtedly, the number of agents in this group is tremendous, and in my opinion, will turn out to be one of the largest and most complex groups of viruses existing in the world. Young virologists, epidemiologists, and others who are searching for a fruitful area of research and discovery should consider the opportunities in investigations of these viruses.

Prevention and Control

For most members of this large group of agents, at present there is no organized method of control. Discussion, therefore, is limited largely to the principles of potential control.

Under certain circumstances vector control is the most logical and practical preventive measure for some agents. Its effectiveness has been well established for yellow fever and dengue in urban areas through the eradication of *Aedes aegypti* mosquitoes. Control of *Culex tarsalis*, the principal vector of western encephalitis and St. Louis encephalitis in the San Joaquin Valley of California, has been attempted for a number of years, in part resulting from the stimulation of our studies. *C. tarsalis* has protean breeding habits, and a great deal of research has gone into the study of its ecology. Control methods have been developed which are generally practical but expensive. Nevertheless, endemicity in the valley is of sufficient importance that control has become imperative. Reeves and I recently summarized the evidence of the effectiveness of this control in a monograph now in press, covering studies carried out from 1943 through 1952. We consider that the evidence is adequate to indicate that vector control has had a definite effect in reducing the incidence of human disease.

For many years the Russians have carried out some degree of control on vectors of the Russian spring-summer tickborne group of viruses in certain endemic forest areas. This is most difficult and expensive, but in their experience these measures are justified.

Artificial immunization of human populations against these viruses is in its infancy. Both active and passive immunization have been considered.

Active immunization with a live attenuated viral agent has proved highly effective for yellow fever. As the only practical method in jungle areas, it is widely applied to travelers entering and departing from recognized endemic areas. In the experimental stage are several other attenuated viral agents for human use which look quite promising. They include Venezuelan encephalitis virus and Rift Valley fever virus. We have in the laboratory of the University of Pittsburgh Graduate School of Public Health at the present time an attenuated strain of Japanese B encephalitis virus, the result of several years of effort to obtain attenuation of an adequate degree. We are almost ready to undertake limited human trials with this strain.

Several formalin-inactivated virus vaccines have had extensive field trials, some apparently with reasonable success. The Russians for many years have employed a formalinized mouse brain vaccine for the Russian spring-summer encephalitis virus, apparently with considerable success. But the protection it offers is limited, and its use has not been free from accidents because of sensitization with central nervous system tissues from the mouse brain. Russian scientists are currently exploring inactivated tissue culture preparations. Our military services used an inactivated mouse brain or chick embryo vaccine for Japanese B encephalitis for several years but abandoned this practice because the degree of effectiveness was not that expected. Formalin-treated chick embryo vaccines for western, eastern, and Venezuelan encephalitis viruses have been used extensively and with apparent success in horses.

During recent years evidence obtained by many of us concerning cross immunity produced by certain viruses to others within the same immunological group lends a certain amount of optimism to prospects for control by active artificial immunization, particularly with the live attenuated viral agents. There is some evidence, for example, that the new attenuated Venezuelan virus vaccine will produce in horses immunity not only to the homologous virus but also to western and eastern encephalitis viruses. In laboratory animals we have shown that immunization to one or two members of Casals' group B viruses with live virus will provide at least a moderate degree of protection against several others in the same immunological group. If the live virus immunization is supplemented with one or two injections of killed virus vaccine prepared from another member of the group, the breadth of immunity is extended still further.

Passive immunization with gamma globulin from immune individuals or from hyperimmune animal serums has proved effective in laboratory animals and is frequently used for accidents occurring among laboratory workers. Certainly, there are instances in which its use is justified. It has never been evaluated for large-scale use, and the short period of protection offered by such immunization makes it unlikely that it will find many fields of practical application.

Control of the transportation of these viruses by air, land, or sea vehicles has been attempted. Some international measures now required are not adequately enforced, and some methods employed are relatively ineffective. With the possible exception of yellow fever vaccine for man, there is little control, or even attempted control, of the movement or shipment of potentially infected vertebrates including man. Much more research is required before there can be an extension of this type of control to other viruses in the group.

At present there is no obvious way of controlling the flight of birds which are infected and viremic, or the possible vectors which they may carry. More data concerning this could be acquired, but even with such knowledge effective control appears unlikely.