

EPIDEMIOLOGY OF THE ARTHROPOD-BORNE VIRUS ENCEPHALITIDES

A PAN AMERICAN PROBLEM*

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In recent years it has become increasingly apparent to those of us engaged in studies on the epidemiology of the arthropod-borne virus encephalitides in the United States that we were not alone in our interest in this problem, but that it has become what I would call a Pan-American problem. This has been evidenced by the constant increase in number of scientific papers on the subject emanating from Latin American countries, and by the ever-increasing number of young scientists from Mexico, Brazil, Argentina, Panama, etc., who have come to our laboratories to increase their knowledge of the techniques necessary for further investigations.

At this time I would like to discuss briefly our present knowledge of these encephalitides and to consider the problems confronting us if we are to progress in our attempts to unveil the basic epidemiological pattern in these diseases. Our ultimate goal, I believe we will agree, is the development of satisfactory methods of controlling the infection as a public health measure for the protection of man and his domestic animals.

Before considering the details of the epidemiology or natural history of the encephalitides let us consider the types now known to be in the Americas, their distribution and on an historical basis their importance to public health.

In the Americas we are now concerned with four well known and widely disseminated viruses, which are known to be arthropod borne, and capable of producing encephalitis.

1. The Western equine virus.—This virus was first isolated from the brain of a horse in California in 1930. Subsequently, in 1938, it was shown to produce disease in man. In the United States this virus is now known to occur in all the Western states and extends eastward into Alabama in the south and Michigan in the north. In the period 1935 through 1944 over 500,000 cases in horses were reported to the United States Bureau of Animal Industry, and it was estimated that there were not less than 1,000,000 cases with 300,000 deaths. As you can readily see, this problem has serious economic implications. Annual epidemics

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in man caused by this virus have occurred in Far Western states in the United States, with the 1941 epidemic of over 3,000 cases in Minnesota, North Dakota, South Dakota and adjacent states being the worst to date. In California outbreaks occur annually in the San Joaquin and Sacramento valleys.

The virus has been reported from the southern border states of California, Arizona, New Mexico and Texas, yet the only report of its isolation south of the United States is from Argentina. I cannot believe this is any indication of the full distribution of the virus, but rather feel it is an indication of the need for further survey work to determine its distribution between the southern border of the United States and Argentina.

2. The Eastern equine virus.—This virus was first isolated from the brain of a horse in 1933, and later from man. In the United States it occurs in most of the Eastern states, and as far *west* as Texas. It has a very extensive distribution in Latin American countries. Up to the present time it has been reported from Mexico, Panama, Venezuela, Brazil, Argentina and Cuba. Without doubt as further investigations are made its distribution will be found to include many additional Latin American countries.

This virus may produce extensive outbreaks in horse and in man, and is typified by a very high mortality rate. To date it is the only type reported from Mexico, and in 1946 the Eastern equine virus was responsible for an explosive epidemic in man and horse in Panama.

3. The Venezuelan equine virus.—The Venezuelan equine virus was first reported as a disease producing organism of horses in Venezuela and Colombia. In recent years, however, it has been shown to produce disease in man. At the present time its reported distribution is limited to four Latin American countries, Venezuela, Colombia, Ecuador and Trinidad; however, there is no reason to believe it is limited to these countries or that it is incapable of further spread.

4. The St. Louis virus.—The St. Louis virus was first isolated from the brain of a fatal human case in 1933 during an extensive epidemic in St. Louis County, Missouri, which involved over 1,000 human cases and resulted in 221 reported deaths.

It would appear that man is the principal natural host in which the St. Louis virus produces a disease, as compared with the preceding three viruses which also affect the horse. While less is known of the extent of distribution of the St. Louis virus, it undoubtedly has as wide or wider distribution than the other encephalitis viruses. It is known to occur in California, Arizona, New Mexico and Texas, and must certainly have an extended distribution to the south of the border. Evidence has been presented that this virus is active in Africa.

With this general knowledge of the types, distribution and importance

of these viruses, let us consider what is known of their epidemiology at the present time.

EPIDEMIOLOGY OR NATURAL HISTORY OF THE ENCEPHALITIDES

In a study of the epidemiology of a disease such as one of the encephalitides we are concerned with factors involving the pathogen, the range of hosts, the types of vectors and the effect of external environmental conditions on these factors. This can be taken to involve an interest in the pathogen itself, in the host relations of the pathogen (which may or may not result in disease), the dependence of the parasite upon a vector for its transmission, and in the dependence of these relationships on favorable environmental conditions if the pathogen is to survive or spread.

In the early 1930's several persons advanced the hypothesis that insects were the vectors of these diseases. In 1933 Kelsler experimentally transmitted the Western equine type virus with laboratory infected *Aedes* mosquitoes, and by 1940 nine species of *Aedes* had been reported as laboratory vectors. Parallel studies with the Eastern equine virus resulted in similar findings. All attempts that were made in the United States to transmit St. Louis virus by mosquitoes gave negative results. Several attempts were made to find naturally infected *Aedes* mosquitoes or other arthropods during epidemics of encephalitis, but without success.

From 1941 through 1946 many advances in our knowledge of the epidemiology of these diseases were made. During this time it has been my good fortune to be a member of a research unit of the Hooper Foundation for Medical Research of the University of California, which has carried out field studies on the encephalitides of man and horse in six Western states of the United States, and I would like to review our findings as a basis for discussion of the future trends of research on these diseases and the possible means of controlling them.

In these studies over 200,000 field-collected blood-sucking arthropods have been tested for virus infection, and Western equine and St. Louis viruses have been isolated more than 100 times from this material. In a search for possible vertebrate reservoir hosts, over 2,000 blood samples from wild and domestic animals have been tested for immunity to one or more viruses.

The first mosquitoes were found infected in nature in the Yakima Valley, Washington, in the summer of 1941 during an epidemic in man and horse. Numerous isolations of Western equine and St. Louis virus were made from *Culex tarsalis* and none from other species of mosquitoes. *Culex tarsalis* had never before been suspected of being a disease vector, but rather was thought of as a pest mosquito. During the same season, strong evidence was obtained which indicated birds were important hosts of the virus in the same area.

Within the next year it was demonstrated that *Culex tarsalis* became infected with Western equine or St. Louis viruses if permitted to feed on laboratory inoculated birds. These infected mosquitoes, if held 8 to 30 days at high summer temperatures, were then found to be capable of infecting other birds by their bite. At no time did the infected birds appear ill. It was shown that the birds had a blood-stream infection for several days with no apparent ill effects and then became immune.

In subsequent studies in the Yakima Valley, Washington, and Kern County, California, a large proportion of the *Culex tarsalis* population was found to be infected. Only an occasional specimen of *Culex pipiens*, *Culex stigmatosoma*, *Aedes dorsalis*, *Culiseta inornata* or *Anopheles freeborni* was found to be infected. In Manitoba, Canada, *Culex tarsalis* and *Culex restuans* have been found naturally infected with Western equine virus. It must be mentioned that some species of mosquitoes which have been found infected in nature have later been shown to be incapable of transmission. Thus the species may be infected, but will not become infective.

In studies in these epidemic areas it was found that 25 to 50 per cent of the domestic fowl were immune to the Western equine and St. Louis viruses which warranted the assumption of past infection.

Investigation of the feeding habits of the various mosquitoes in these areas by application of the precipitin ring test to over 1,000 wild-caught, blood-engorged mosquitoes, showed the *Culex tarsalis* fed principally on birds. Next in order of choice were cow, horse and man. The *Aedes* mosquitoes showed preference for horse and cow blood, rarely feeding on birds.

Available evidence indicated that in large mammals, St. Louis and Western equine viruses did not commonly appear in the blood stream in sufficient amounts for infection of mosquitoes.

As a result of these studies it appeared that the fundamental biologic cycle or infection chain for the Western equine and St. Louis viruses in the regions surveyed was bird-mosquito-bird, and that occasionally an aberrant infection occurred in horse or in man through the bite of one of these infected mosquitoes.

Man and horse, the two hosts showing disease, were apparently accidental, but not infrequent entrants into the infection chain, but there was no evidence that the virus was dependent upon these hosts for its survival. Thus is brought to mind the comparable position of man in the epidemiology of Jungle Yellow Fever.

The relative importance of wild birds in the epidemiology of these viruses is still uncertain. However, there are strong indications that the small Passerine birds, such as finches and possibly sparrows may play an important role.

The following facts substantially support the great importance of the role played by fowl and *Culex* mosquitoes in the infection chain of the Western equine and St. Louis viruses: the large amount of virus found in the blood of infected birds; transmission by the bite of *Culex tarsalis* from fowl to fowl in the laboratory; finding of up to 50 per cent of the domestic fowl with antibodies to the Western equine and St. Louis viruses in certain epidemic areas; the special predilection that *C. tarsalis* has for the blood of fowl; and finding this mosquito naturally infected over 100 times in three widely separated Western states.

It is of interest to note that the reported occurrence of this vector closely parallels the known distribution of these two viruses at the present time in the United States. It must always be remembered, though, that the possible range of mosquito vectors is great, and it could well be that in future studies, species other than *Culex tarsalis* will be proven to be important vectors. For example, for the Western equine virus, we have found five other species of mosquitoes (four genera) infected one or more times, and thirteen species of mosquitoes (3 genera) have been shown to be capable of experimental laboratory transmission.

In recent years mites parasitic on wild and domestic birds have been found infected with Western equine and St. Louis viruses and may well be involved in bird-to-bird transmission, even though not involved in transmission to man. Such a means of transmission could be of great importance in maintenance of endemicity in an area and also of possible importance in some areas are the "kissing bugs" (*Triatoma*) of which *Triatoma sanguisuga* has been found naturally infected with Western equine virus in Kansas. Several *Dermacentor* ticks have been shown to be capable of transmission experimentally.

As you have noted most of this discussion has been devoted to the epidemiology of the Western equine and St. Louis viruses, and very little has been said concerning the Eastern or Venezuelan viruses. The reason for this is that comparatively little field investigation has been carried out on the latter. On the basis of laboratory studies, many species of *Aedes* are known to be potential vectors of the Eastern equine virus. Birds are commonly infected, and may even show clinical symptoms. For the Venezuelan virus *Mansonia titillans* has been shown to be naturally infected and may easily be infected by feeding on sick horses. However, until more careful studies are made under field conditions, our knowledge of the epidemiological picture in its entirety will be incomplete.

CONTROL OF ENCEPHALITIDES

In justifying the organization of a program for the control of the encephalitides, we should not lose sight of the fact that they are not only

diseases of man, but certain types also constitute very important diseases of equines. Any one of the four types now known in the Americas possesses epidemic potentialities in man, as is evidenced by their history.

These diseases may conceivably be attacked at any link in their infection chain. Let us evaluate the various possibilities.

1. Vaccination of clinically susceptible mammalian hosts.—Effective vaccines against the Western, Eastern, and Venezuelan viruses have been developed for man and horse, and proper immunization will protect against the virus for at least one year. However, unless the types of viruses active in an area are known with certainty, vaccination can only be applied on presumptive grounds, and appearance of a second type of virus in an area where only one was believed to occur can and has led to serious horse epizootics. Obviously the determination of the types of virus active in any area depends on the work of field public health workers and veterinarians in close cooperation with a virus laboratory. Whenever possible, autopsy material should be submitted to the virus laboratory as a check on which viruses are present in the area of interest.

As a potentiality, let us look at the situation in Mexico. Eastern virus has been shown to be here, and I dare say horses which are of great value are vaccinated against it. However, the Western equine virus is known to occur in the border states of the United States and the Venezuelan virus to the south. There is always the possibility of these already being, or appearing, in Mexico, and if they do, vaccination against the Eastern type only will not protect the horses.

Our present knowledge of the efficacy and value of human vaccination does not indicate its use as a protective measure, except under certain conditions. In man, the morbidity rates in the reported outbreaks have usually been so low that on the basis of average yearly incidence of clinical disease, vaccination has not been recommended. In addition, a vaccine for the St. Louis type has not been available.

Probably of greatest importance is the fact that even if all horses and men in an area were immunized for several years against the equine viruses, the essential bird-mosquito-bird infection chain for the Western equine type, at least, would not be disturbed, and on termination of the vaccination program and immunity, the disease would reappear.

2. The Control of Avian Hosts.—The control of the infection in domestic or wild birds by vaccination or eradication is obviously not feasible. The importance of birds in the spreading of the encephalitis viruses from one area to another has not been evaluated, and until some method of investigating this potentially important factor has been developed, it cannot be considered.

3. The Control of Arthropod Vectors.—The one approach which offers the most hope of success and still one that is possibly practical, is a program directed against the mosquito vectors. The successful control

measures developed for malaria, epidemic yellow fever, and dengue fever, are outstanding examples based on this same premise. Granted, we are faced with a more diverse infection chain than in the case of these three diseases.

The primary requisite to such a program in any area is the determination of the particular vector or vectors so that immediate steps can be taken to develop and carry out control measures aimed at these vectors. Once the vectors are determined, their biology must be studied and on the basis of such study practical control methods developed to fit the needs.

As an example, the California State Department of Public Health has evaluated the situation in California and concluded that the Public Health importance of the encephalitides and our present knowledge of their epidemiology and possible methods of control warrants such a program. A sum of \$600,000 was appropriated by the State Legislature for the first two years' activities. Money from this fund is being allocated to those mosquito abatement districts which lie in endemic encephalitis areas. These funds are to be used in the development of programs directed specifically at the encephalitis vectors over and above the normal mosquito control program of a district. These funds are permitting mosquito abatement districts to employ trained entomologists, additional premise inspectors, and control crews, to be used on *Culex tarsalis* control, to an extent that pest mosquito abatement activities in many instances could not afford, even were such personnel available. As a result, new methods of attack on this species are being developed, which its former status, as a relatively minor pest mosquito, did not warrant.

THE FUTURE PROBLEM IN THE AMERICAS

To anticipate and plan to meet any future public health problems is the aim of any sound public health program. In the case of the encephalitides, we are in the process of evolving a basic plan for their control. Our present knowledge indicates that an attack on the known mosquito vectors offers the greatest promise of success in California, an area where extensive preliminary investigations were carried out before such a program was put into effect. The findings from these investigations and programs can not be applied to the problem in Mexico, without reservations. For example: in Mexico, some 114 species of mosquitoes have been reported. Of these, only twelve have been tested in the laboratory for their ability to act as vectors of the encephalitis viruses; and all the tests have been made in United States laboratories, thus discounting the possibility of geographical differences in the species. Nothing is known of the vector ability of many of your most common mosquitoes: for example, species of *Psorophora*, *Mansonia*, and *Haemagogus*: or, indeed, most species of *Culex* or *Aedes*. The relative vector ability of the vari-

ous common species of mosquitoes in any area must be determined as a basis for encephalitis control. The animal hosts may also vary from one area to another, and indeed in many cases your most common birds might be species which do not even occur in California.

In the United States, we are concerned with the further development of our knowledge of the epidemiology of our virus encephalitides as a basis for control in the event of future epidemics. We feel certain phases of our knowledge are still incomplete, and much is left to be exposed. As an example, in recent years we have isolated from mosquitoes what appears to be a new virus, which we are calling the "California" encephalitis virus. Its importance as a pathogen of man or other animals is still to be determined; little is known of the range of its mammalian, avian, or arthropod hosts, and nothing is known of its geographical distribution.

In recent years workers in Colombia isolated from mosquitoes what appear to be three new viruses capable of producing encephalitis in experimental animals. These were designated as *Anopheles* A, *Anopheles* B, and *Wyeomyia* viruses, after the mosquitoes from which they originated. Nothing is known of their possible importance as pathogens of man or his domestic animals.

Thus it appears that in any area in which intensive work is carried out, new viruses may be found, any one of which must be carefully investigated as a potential pathogen of man and his domestic animals.

A factor of inestimable importance and one which I have previously mentioned, is the future possibility that exotic encephalitis viruses may be introduced into the Americas or that viruses endemic to one area of the Americas may spread or appear in other countries. In California we have been particularly concerned with the possible introduction of Japanese B encephalitis virus from the Orient. We have demonstrated that seven of our common *Culex*, *Culiseta* and *Aedes* could serve as vectors of Japanese B virus, should this occur, and feel that the introduction of this virus into the Central Valley of California could well result in an epidemic.

I have already mentioned the probable appearance or presence of the Western equine, St. Louis and Venezuelan viruses in Mexico. These potentialities should be investigated, if at all possible.

I trust you will not take an alarmist attitude on the basis of these closing statements. The important point is to be acquainted with the problems which face us, and that we develop a program of investigation and attack based on factual knowledge and not be caught unprepared in an emergency.

I have outlined the evidence that arthropods, particularly mosquitoes, are the vectors of certain of the virus encephalitides. It has yet to be

proven that the reduction or elimination of these vectors will eradicate or prevent the spread of the disease to man or equines, or prevent the transmission of virus among the animal hosts. It is probable that a much more complete numerical abatement of mosquitoes than has been found adequate in malaria, filariasis, or epidemic yellow fever, will be necessary for satisfactory encephalitis control.

This problem is a challenge to those of us interested in public health and virus research programs. The complexity of the problem must be borne in mind at all times, if we are to work together and hope for success.

LA ENCEFALITIS VIRAL ORIGINADA POR ARTRÓPODOS: UN PROBLEMA PANAMERICANO (*Sumario*)

En todas las Américas ha despertado gran interés el problema de la encefalitis viral de origen artrópodo. Se repasan los conocimientos actuales sobre virus de las encefalitis equinas del Oeste, del Este y de Venezuela, así como de la encefalitis de San Luis; siendo el huésped principal de los tres primeros tipos el caballo y del último, el hombre. Los estudios realizados de 1941 a 1946, demostraron que el *Culex tarsalis* es un importante vector en los virus equinos del Oeste y San Luis. El ciclo de infección es pájaro-mosquito-pájaro, aunque estos últimos jamás aparecen enfermos. De vez en cuando se han hallado infectados otros tipos de mosquitos. Se han efectuado relativamente pocas investigaciones con los virus de los tipos Este y Venezolano. Entre las medidas de control, Reeves considera impráctica la vacunación de los huéspedes mamíferos debido a la falta de conocimiento de los tipos de virus presentes en una localidad y tiempo determinados, y considera impracticable el control de los huéspedes ovejunos. Cree Reeves que el control de los vectores artrópodos (especialmente el mosquito) es el que ofrece mayor esperanza de éxito. El Depto. de Sanidad del Estado de California, está invirtiendo \$600,000 en el control de *Culex tarsalis*. Aún falta realizar gran número de investigaciones antes de poder desarrollar un programa de control para las Américas.

Exposición al cloro.—Los AA. repasan las observaciones acumuladas en 33 de los enfermos hospitalizados después de la exposición accidental al cloro, en Brooklyn, en junio de 1944, encontrando que los síntomas durante las primeras horas después de haber estado sometidos a la acción del cloro consistían en: ardor de los ojos, con lagrimeo; ardor de la nariz y boca, con rinorrea, y aumento de la secreción salival; tos, sensación de ahogo y dolor subesternal. Frecuentemente estos síntomas fueron acompañados de náuseas, vómitos, cefalea y malestar general. Los cambios en las vías respiratorias consistieron en tráqueobronquitis, edema pulmonar y neumonía. Once de los 33 enfermos observados por 16 meses después de dados de alta no presentaban síntoma alguno. Diez y seis enfermos tenían reacciones como fobias, fenómenos histéricos y disfunciones psicomotrices persistentes.—Jour. Am. Med. Assn., 900, mzo. 27, 1948.