ARTICLES

A MEMORIAL TO FINLAY, REED, GORGAS AND SOPER AS MAJOR CONTRIBUTORS TO PRESENT DAY CONCEPTS ESSENTIAL FOR CONTROL OF MOSQUITO-BORNE ARBOVIRUSES[1, 2]

WILLIAM C. REEVES

Department of Biomedical and Environmental Health Sciences, School of Public Health,
University of California, Berkeley, CA 94720

It is a privilege to memorialize the contributions that Carlos Finlay, Walter Reed and William Gorgas made to our understanding of the epidemiology and control of diseases caused by mosquito-borne viruses. As you will see, I have added Fred Soper to this distinguished group. I also took this opportunity to review our present knowledge of vector biology that is critical to the control of epidemics of these diseases in North America.

First, let me review the significance of the early contributions of the above pioneers in this area of science.

The first major discovery relevant to the control of arboviral diseases was in 1900 when Reed (1901, 1902) reported on the Yellow Fever Commission's studies in Cuba. The studies were based in large part on the observations and hypotheses developed by a Cuban, Carlos Finlay. The Yellow Fever Commission reported that they had transmitted yellow fever from man to man by the bite of a mosquito *Aedes aegypti*. Gorgas (1911) quickly applied these findings in a program for control of *Ae. aegypti* and successfully eradicated yellow fever from Cuba where it had prevailed for over 150 years. Control of this major mosquito-borne disease depended on the finding and removal or treatment of almost every breeding source of the vector in the domestic environment. The principle was to reduce the vector population below the threshold level essential to maintain the viral transmission cycle.

Subsequently, eradication of *Ae. aegypti* became the focus of a major program of the Rockefeller Foundation led by Fred Soper (1943). For practical purposes yellow fever was controlled and eradicated from major urban centers of the World where it had prevailed for over a century. However, the discovery of jungle and rural cycles of yellow fever in the Americas and Africa (Strode 1951) put a damper on the hopes of yellow fever eradication and explained the reappearance of virus in urban centers where it had been eradicated. Subsequently, an effective vaccine was developed (Thieler and Downs 1973) and this provided an alternative approach to protect rural populations in areas where vector control was impractical.

The point of the preceding brief historical review was to emphasize that for over 80 years we have understood the epidemiological factors that control the spread of a major mosquito-borne viral disease. Studies over the past 40 years have extended this knowledge to a wide array of other arboviruses including the demonstration that prevention and control of epidemics caused by such agents is feasible by vector control although it is expensive.

---

[1] Fourth annual AMCA Memorial Lecture delivered before the American Mosquito Control Association, Sacramento, California, April 19, 1982.

[2] Acknowledgment is made to the Lowndes Engineering Company, Inc. for its participation in sponsoring the 1982 Memorial Lecture.

My concern is that permanent and effective control programs for mosquito-borne viruses are non-existent in most areas even though we continue in a most impressive fashion to add to our epidemiological knowledge of the diseases associated with mosquito-borne viruses and have extended our degree of sophistication regarding the vectors and the causative viruses.

The above background on yellow fever in its urban cycle serves well for an extension of this discussion to dengue fever. It has been known since 1902 (Graham 1903), that dengue fever was a viral infection transmitted in an urban cycle by *Ae. aegypti.* In recent years it was found that 4 distinct viruses can cause the disease; that the infection spectrum goes from inapparent infection through febrile illnesses to hemorrhagic fever, shock syndrome and death; and that there are alternative vectors to *Ae. aegypti* particularly in the Pacific area. None of these important findings has changed the basic concept that developed from the yellow fever studies, namely, that reduction of the vector population to levels that cannot support the transmission cycle is the most feasible approach to control. In spite of this knowledge, the dengue fevers continue to occur at endemic or epidemic levels or are reintroduced repetitively over extensive areas of Asia, the Pacific and Caribbean islands, and South and Central America. As a further expansion of this concern, an *Ae. aegypti* control and eradication program was making excellent progress in the United States in the 1960's (Smith 1967) when our government decided that it was costing too much and was not that important. The annual budget in 1968 was 16 million dollars and 2,610 persons were employed. For practical purposes, the program was abandoned within 2 years. Major urban centers in the southeastern United States now report that *Ae. aegypti* is a major pest and I assume that these are potentially receptive areas for dengue and yellow fever.

Until recently the occurrence of dengue was referred to as a problem of the underdeveloped areas of the World. If this is the case, we can now include parts of Texas and Queensland, Australia in that classification as dengue virus was reintroduced into those areas and they were receptive as there was an adequate population of *Ae. aegypti* to support transmission and there was a susceptible human population.

Arbovirus epidemiologists were not surprised and had anticipated these developments. The point is that there was no concerted effort to carry out the principles of vector control that were established by Gorgas and Soper. A dengue fever epidemic was reported recently in Cuba with over 300,000 cases and 158 deaths. This could not have happened in the early 1900's at the time of Gorgas' successful vector control program. The response of the Cuban government is noteworthy and is reported in detail in the Epidemiological Bulletin of the Pan American Health Organization (Anonymous 1982). The Cuban Government has established a program that can serve as a model for complete response which includes island-wide house-to-house search for and eradication of *Ae. aegypti* which is being supplemented by island-wide applications of organophosphorous insecticides. I recommend the above report as essential reading. Few countries in the Western Hemisphere are prepared to meet the inevitable high cost of such a program today. I would add that dengue virus infections have remained endemic in Puerto Rico and Southeast Asia since the 1960's in spite of any efforts to establish control programs.

I have expressed concern previously (Reeves 1972, 1980) as have others (Downs 1981), that areas where dengue viruses prevail are potentially receptive to yellow fever. A recent conference on yellow fever (Woodall 1981) reiterated this concern and recommended the use of 17D vaccine in the event of an epidemic. However, further study revealed that only 7 million doses of the vaccine were available in the world and that this supply probably could not be doubled in the event of an epidemic. That amount of vaccine will not control yellow fever if it is introduced into major urban centers in the Americas, Asia or Africa. Similarly, there is little chance that effective vaccines for other arboviruses will be available in large amounts in the near future.

I do not believe that the failure to control dengue or yellow fever is for lack of knowledge on the populations at risk, the causative viruses or which mosquitoes are vectors. In February of this year I presented a paper (Reeves 1982) at the International Seminar on Viral Diseases in South-East Asia and the Western Pacific on the expanding gap between the epidemiological knowledge of arboviruses and their effective control. I concluded that vector control programs were ineffective becaue of:

1. A primary dependence on insecticides rather than source reduction for vector control.
2. Legal restrictions on the use of insecticides and lack of a legal basis for water resource management in both urban and rural environments.
3. A limited knowledge of vector behavior that is essential for control of the adult female population that is transmitting infection.
4. A low priority by political bodies for funding of control programs due to lack of belief by the public that there is a need for action until an epidemic is in progress or a pest population is out of control.
5. An acute shortage of adequately trained persons to investigate the problems and initiate effective control programs.

I believe that these comments are equally applicable to control of the mosquito-borne viral diseases that prevail in North America and that concern the majority of this audience. What are my thoughts on the problem?

Western equine encephalomyelitis (WEE), Eastern equine encephalomyelitis (EEE), St. Louis encephalitis (SLE) and representatives of the California encephalitis (CE) complex are the principal mosquito-borne viral diseases of concern in North America. On an international scope we could add Japanese encephalitis, Murray Valley encephalitis, West Nile, Venezuelan equine encephalitis and other diseases as examples. These infections differ from yellow fever and the dengues in that they rarely or never are spread from man to man by a vector but rather depend on transmission between wildlife hosts or transovarial infection in their vectors for their basic maintenance. Spread to man is an accidental event and of no importance in viral perpetuation. Regardless of that, the principles developed by Gorgas and Soper apply—reduce the vector population to threshold levels below that required for effective transmission if you wish to prevent epidemics. To accomplish that objective, requires the establishment of a long-range program of vector abatement backed up with a surveillance system and a capacity to act rapidly when environmental conditions provide a warning of impending epidemics that will require emergency abatement of large adult vector populations.

Detailed epidemiological studies of WEE and SLE in California (Reeves and Hammon 1962) provided a basis for development of a state-wide surveillance program in California in the 1960's. Similar programs, each tailored to fit the epidemiological variations of the different mosquito-borne viruses that prevail, are now established in at least 18 states and several provinces in Canada. The Vector-Borne Viral Diseases Division of the Centers for Disease Control summarizes information that is gathered into their Encephalitis Surveillance Reports. The 6 types of information that represent the core content of an arboviral surveillance program (Reeves and Milby 1980) are knowledge on:

1. Water availability from precipitation and other water resources that are available for vector production.
2. Occurrence of temperatures that favor or disfavor development of

vector populations and viral development in those populations.
3. Monitoring the levels of the primary mosquito vector populations.
4. Viral activity in: a) Vectors, b) Sentinel hosts and c) Clinical cases.
5. The economic manpower and equipment resources available for routine and emergency vector control programs.
6. Assessment of the probable effectiveness of alternative programs to control the adult female vectors that are infected and are transmitting infection.

It must be emphasized that surveillance is based on information gathered at and used by agencies concerned with control at the local level. Centralized reporting and services at the state or national level only serve to spread knowledge and to extend the system to a broader geographical area.

The experiences in Kern County, California in 1958 (Reeves et al. 1964), Dallas, Texas in 1966 (Hopkins et al. 1975) and Manitoba, Canada in 1981 demonstrated how impending or in-progress epidemics of WEE and SLE can be attacked and how important a surveillance program can be. There is no reason to question that the emergency control of vector populations in these and other epidemics had a desirable effect. At the same time I believe that we learned certain lessons from these experiences.

When emergency control programs have to be instituted in an epidemic, the cost of human suffering is already high. There were 15 WEE and 2 SLE cases in Kern County, 145 cases of SLE in the Dallas epidemic and 25 cases of WEE in Manitoba. Cases will have occurred and other individuals will be in the incubation period when the emergency program is started. Such programs are expensive—almost $2,000,000 was spent to apply ULV Baygon (propoxur) by air over an area of 450,000 hectares (over 1,000,000 acres) in Manitoba. Programs can also be ineffective because of insecticide resistance of the vector or delays in action by endless debate over the health implications of insecticide exposure or regulations that limit the use of effective insecticides. However, we have come a long ways from the 1950's and 1960's as we now know that control of the adult female vectors that are infected and are transmitting infection is the only measure that will immediately abate an epidemic of WEE or SLE. Ultra-low volume aerial application of insecticides is the current method of choice to control such epidemics. Elimination of the infected and infective mosquito population over a large geographic area for the 4–5 day period of viremia in vertebrate hosts will eliminate the etiological reservoir and prevent new infections in the vectors and transmission to humans.

I want now to identify some areas of research on the biology of vectors of arboviruses that will further our knowledge of the epidemiology of these infections and improve programs to control the diseases. In the interest of time, I will present concepts and problems rather than detailed data.

The ovaries of female mosquitoes contain markers that allow us to separate nulliparous from parous individuals. These markers can be used in combination with fluorescent dusts in mark-release-recapture studies to make estimates of adult survivorship and population levels (Milby 1979, Nelson et al. 1978, Nelson and Milby 1980). The resulting life tables have contributed to our understanding of the dynamics of viral transmission and led us to fully appreciate that the older viral transmitting females are relatively few in the population and should be the primary target for control in the event of an epidemic.

However, there is a gap in our knowledge if we wish to implement such programs. I do not know of any current in-depth field research to determine if the usual ultra-low volume applications of insecticides for adult mosquito control are equally effective against parous and nulliparous females, old versus freshly emerged females, or females derived from insecticide resistant versus susceptible larval populations. Such data are essential if the objective of epidemic control is to eliminate the older adult vector population and interrupt viral transmission.

Tests of mosquito pools for viral isolations is a most important aspect of surveillance programs. However, little attention has been given to the collecting techniques for such pools. A method may be selected because it is easy and will provide large samples rather than be a technique that will assure that the samples contain significant numbers of the feeding parous females that can be infected and transmit virus. There is little purpose in testing large numbers of freshly emerged nulliparous females unless one is looking for transovarially transmitted viruses.

If a vector control program is to be effective and epidemics are to be controlled, it is essential that the primary vector species be identified for each virus in the area of concern. We used to assume that the isolation of virus from a species was sufficient reason to condemn a species as a vector. We now know this is not so as studies on vector competence (Hardy et al. 1979) have shown that many species that feed on infected vertebrate hosts will ingest virus but are ineffective vectors. A significant number of even the most efficient primary vector species can be infected with but never transmit viruses effectively. The following experiences illustrate the problem. We have observed that the levels of WEE viral transmission can remain low or be undetectable in a *Culex tarsalis* population that has risen to a high level over an extensive area (Reeves 1970). This was contrary to our earlier epidemiological experience and required an explanation. We also had observed that in years of high levels of viral transmission an average of only 1 in 4 *Cx. tarsalis* infected with WEE virus could transmit infection (Reeves et al. 1961). It seemed unlikely that a failure to have completed the extrinsic incubation period was a sufficient explanation for these observations.

Studies have revealed there are wide variations in the vector competence of *Cx. tarsalis* subpopulations for WEE virus (Hardy et al. 1976). Subpopulations have been selected from a single colony that are either highly resistant to or highly susceptible to WEE viral infection and resistance is a recessive genetic trait (Hardy et al. 1978). To our surprise, many *Cx. tarsalis* that became infected when fed on low titer viremias never transmitted infection by bite even though the virus multiplied to high levels after incubation for over 21 days at high temperatures. These studies revealed that there were dose-dependent gut and salivary gland barriers that limited vector competence (Kramer et al. 1981). The studies are now extended into very sophisticated evaluations of the influence on viral infection of cell receptors, cell membranes, enzymes, inhibiting substances in haemolymph and various temperatures of incubation in the vector.

Extrinsic incubation temperatures have profound effects on the growth of different viruses in their vectors. It is interesting that no studies on extrinsic incubation of arboviruses have been done in climate chambers that duplicate the fluctuating temperatures where vectors live. Such studies could lead to exciting and unexpected results.

Dr. Hardy and associates are studying the interesting question of why *Cx. tarsalis* is the primary vector of SLE virus in the Western United States while the *Culex pipiens* complex, although abundant in the same area, is a secondary vector at best. In contrast, in other parts of the United States the *Cx. pipiens* complex is a primary vector of SLE virus during epidemics (Monath 1980). Vector competence studies indicate that *Cx. tarsalis* is an efficient vector of SLE viral strains collected from a wide range of areas in the United States. It has few salivary gland barriers to efficient transmission. In contrast, *Cx. pipiens* from California is an inefficient vector of California viral strains as compared with *Cx. tarsalis.* There are several hypotheses to explain these differences which are under study. The significance is that with confirmation we will be able to concentrate vector control programs in California and other western areas on the competent *Cx. tarsalis* even though *Cx. pipiens* are abundant.

Field studies on the life table of adult female *Cx. tarsalis* combined with the studies on vector competence have made us realize how tenuous viral transmission cycles can be. We find for *Cx. tarsalis* that the fertility rate of females, survival of immatures and resulting numbers of adult females is quite low as compared to the average of over 150 eggs deposited per female at each oviposition. Once an adult female emerges she does not mate until 24 to 48 hours of age. If autogenous, she delays the first blood-meal until oviposition of those eggs 4 to 5 days later. Her first possible contact with a viremic blood-meal is at 3 to 6 days of age and the majority of such meals will not be viremic. Meanwhile, daily mortality or losses from the resident vector population by dispersal may range from 25 to 40% per day (Nelson and Milby 1980, Nelson et al. 1978). Even if infected with virus, a surviving female probably will oviposit and seek the next blood-meal within 5 to 7 days at which time she may not have completed extrinsic incubation so she cannot transmit infection. She must take a third blood-meal and be a competent individual who has passed virus in infectious quantities into the salivary glands and the host must be susceptible to infection or the cycle is broken. This biological situation is so tenuous that you must wonder how arboviruses persist and why they are so hard to control, but they do. However, this background increases our confidence that detailed knowledge of the interaction of biological variables is the basis for planning the most efficient vector control program. The older viral transmitting female vector populations are clearly identified as the primary target in the event of an epidemic. An effective adulticiding program should increase daily mortality to over 90% which should stop the viral transmission cycle.

I could extend this discussion to consider the importance of genetic studies on vectors, other types of biological studies and statistical modelling of vector populations but time will not permit. Sufficient to conclude this section with my belief that many such areas can still be studied profitably to improve control programs and epidemiological studies. We have a wide array of new techniques that can contribute to the studies. Until recently, it has been relatively easy to obtain funds for basic laboratory research on vectors and to train students and staff, but this is no longer true. It has always been and will continue to be difficult to obtain adequate funding to put into operation and maintain effective control programs. So, I reiterate the point I made at the opening of this paper, that we have the basic tools to extend our epidemiological knowledge and to implement effective control programs but must continue to develop more complete knowledge and increased control efficiency in those programs.

I believe that we must all make an effort to influence the public and its elected officials to utilize present knowledge for effective control of arboviral diseases. Such action is a most fitting memorial to the contributions of Finlay, Reed, Gorgas, Soper and their successors.

References Cited

Anonymous 1982. Program for dengue elimination and *Aedes aegypti* eradication in Cuba. Epidemiol. Bull. PAHO 3:7–10.

Downs, W. G. 1981. A new look at yellow fever and malaria. Am. J. Trop. Med. Hyg. 30:516–522.

Gorgas, W. 1911. A few general directions with regard to destroying mosquitoes particularly the yellow-fever mosquito. Wash. Gov. Printing Office Document 822.

Graham, H. 1903. The dengue: a study of its pathology and mode of propagation. J. Trop. Med. London 6:209–214.

Hardy, J. L., G. Apperson, S. M. Asman, W. C. Reeves. 1978. Selection of a strain of *Culex tarsalis* highly resistant to infection following ingestion of Western equine encephalomyelitis virus. Am. J. Trop. Med. Hyg. 27:313–321.

Hardy, J. L., W. C. Reeves and R. D. Sjogren. 1976. Variations in the susceptibility of field and laboratory populations of *Culex tarsalis* to experimental infection with Western equine encephalomyelitis virus. Am. J. Epidemiol. 103:498–505.

Hardy, J. L., W. C. Reeves, J. P. Bruen and S. B. Presser. 1979. Vector competence of *Culex tarsalis* and other mosquito species for Western equine encephalomyelitis virus. *In* Arctic and tropical arboviruses (E. Kwistak, Ed.) Acad. Press, New York, pp. 151–171.

Hopkins, C. C., F. B. Hollinger, R. F. Johnson, H. J. Dewlett, V. F. Newhouse and R. W. Chamberlain. 1975. The epidemiology of St. Louis encephalitis in Dallas, Texas, 1966. Am. J. Epidemiol. 102:1–15.

Kramer, L. D., J. L. Hardy, S. B. Presser and E. J. Houk. 1981. Dissemination barriers for Western equine encephalomyelitis virus in *Culex tarsalis* infected after ingestion of low viral doses. Am. J. Trop. Med. Hyg. 30:194–201.

Milby, M. M. 1979. The mark-release-recapture study as a research technique. Proc. Calif. Mosq. Vector Control Assoc. 47:83–85.

Monath, T. P. 1980. St. Louis encephalitis. American Public Health Association, Wash. D.C.

Nelson, R. L. and M. M. Milby. 1980. Dispersal and survival of field and laboratory strains of *Culex tarsalis* (Diptera: Culicidae). J. Med. Entomol. 17:146–150.

Nelson, R. L., M. M. Milby, W. C. Reeves and P. E. M. Fine. 1978. Estimates of survival, population size and emergence of *Culex tarsalis* at an isolated site. Ann. Entomol. Soc. Am. 71:801–808.

Reed, W. 1901. Propagation of yellow fever: observations based on recent researches. Med. Record 60:201–209.

Reed, W. 1902. Recent researches concerning etiology propagation and prevention of yellow fever, by the United States Army Commission. J. Hyg. 2:101–119.

Reeves, W. C. 1970. Current observations on mosquito-borne viruses of concern to mosquito abatement districts in California. Proc. Pap. Annu. Conf. Calif. Mosq. Control Assoc. 38:6–9.

Reeves, W. C. 1972. Can the war to contain infectious diseases be lost? Am. J. Trop. Med. Hyg. 21:251–259.

Reeves, W. C. 1980. William Crawford Gorgas. A view of his contributions to control of selected disease problems in the Americas. Trop. Med. Hyg. News Suppl. 29(3):4–10.

Reeves, W. C. 1982. The expanding gap between epidemiological knowledge of arboviruses and their effective control. Proceedings International Seminar on Viral Diseases in South-East Asia and the Western Pacific. Academic Press Australia. (In press).

Reeves, W. C. and W. McD. Hammon. 1962. Epidemiology of the arthropod-borne viral encephalitides in Kern County, California, 1943–1952. Univ. Calif. Publ. Public Health, Vol. 4. Berkeley: Univ. of Calif. Press, 257 p.

Reeves, W. C. and M. M. Milby. 1980. Assessment of the relative value of alternative approaches for surveillance and prediction of arboviral activity. Proc. Pap. Annu. Conf. Calif. Mosq. Vector Cont. Assoc. 48:3–7.

Reeves, W. C., R. E. Bellamy and R. P. Scrivani. 1961. Differentiation of encephalitis virus infection rates from transmission rates in mosquito vector populations. Am. J. Hyg. 73:303–315.

Reeves, W. C., R. E. Bellamy, A. F. Geib and R. P. Scrivani. 1964. Analysis of the circumstances leading to abortion of a Western equine encephalitis epidemic. Am. J. Hyg. 80:205–220.

Smith, J. 1967. Current status of *Aedes aegypti* eradication in the Western Hemisphere. Arch. Environ. Health 15:137–138.

Soper, F. et al. 1943. The organization of permanent nation-wide anti-*Aedes aegypti* measures in Brazil. Rockefeller Found., New York.

Strode, G. (ed) 1951. Yellow fever. McGraw Hill, New York.

Theiler, M. and W. Downs. 1973. The arthropod-borne viruses of vertebrates. Yale Univ. Press, New York.

Woodall, J. P. 1981. Summary of a symposium on yellow fever. J. Infect. Dist. 144:87–91.