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History of Epidemiological Aspects of Yellow Fever

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This review attempts to follow the trail of the development of epidemiological aspects and concepts of yellow fever and yellow fever transmission (vectors, vertebrate hosts, spacing of epidemic outbreaks) with less emphasis on well-documented early history and more emphasis on epidemiological problems still remaining, plus discussion of possible means of resolving certain of these problems.

History and epidemiology are intertwined. Epidemics of disease have often been of importance in influencing the course of history. Among the diseases contributing in remarkable fashion to the course of human development, yellow fever is outstanding. The book *Yellow Fever* edited by G.K. Strode [1] is a source of epidemiological information relating to the virus, the vertebrate hosts, the vectors, the worldwide distribution of the disease, the development of the vaccines, up to mid-century. Knowledge of this disease is lacking in the centuries prior to the great explorations of the fifteenth and sixteenth centuries and it is not until the seventeenth century that accounts begin to appear which can be assumed to refer to yellow fever. Diagnostic confusion undoubtedly existed in the early centuries, and certainly exists today. Malignant tertian (*P. falciparum*) malaria was prevalent then. Weil's disease (leptospirosis: *Leptospira icterohemorrhagica*) was responsible for diagnostic confusion, not only in the investigations of Hideyo Nuguchi [2] but also today. Profligate Nature has no reserve about interjecting cases of yellow fever and leptospirosis into the epidemic scenario as she does also with malaria, dengue, and other virus diseases. The viral hepatitis infections are an ever-present source of worry for the diagnostician. Hepatitis B virus is very prevalent in a number of African countries, including, for example, Senegal [3], a West African country where yellow fever has surfaced in several quite widely separated localities over the past fifteen years [4,5,6,7]. There are diseases only recently discovered: Lassa Fever [8], Marburg Disease [9], and Ebola Virus Disease [10] which may be confused with yellow fever.

Diagnostic difficulties pose problems in epidemiological interpretations of historical data. Nonetheless, it can be considered certain that the yellow fever epidemics listed in Scott [11], in both Africa and the New World, in large part are yellow fever, and in certain instances—for example, the 7th Fusiliers in the Bahamas—are yellow fever with no possibility of admixture with malignant tertian malaria. The anopheline vector(s) of malaria have a marginal existence on a few of

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the islands and no autochthonous cases of malaria have been reported from the Bahamas [12].

Carter [13] has written on the history of yellow fever. He studied in detail the passage of yellow fever through a community, attempting to define the incubation period of the disease. Josiah Clark Nott, a Connecticut native, settled in Alabama, had opportunity to study yellow fever at close hand in Alabama. In one epidemic affecting Mobile [14], he lost four of his children, even though he had moved them to the country, outside of the stricken city. His observations on epidemic spread led him to postulate an insect vector for yellow fever [15]. His hypotheses are not precise, formulated as they were fifty years before the first demonstration of a mosquito vector of disease. Beauperthuy, a physician working in Angostura (later Ciudad Bolivar), Venezuela, advanced a similar hypothesis several years later [16]. Nott was a keen observer and set forth clearly his views that yellow fever was what we would call today a disease with a wide spectrum of clinical manifestations, ranging from mild illness in many cases, sometimes with no or very low fever, to cases with a fulminating onset, often terminating, in but four or five days, in death. Carlos Finlay, working in Havana, Cuba, advanced again the hypothesis of a mosquito vector of yellow fever [17], and backed up this hypothesis with experimental work, attempting to show that *Aedes aegypti*, then known as *Stegomyia fasciata*, could be infected by and transmit yellow fever. The U.S. Army group in Havana, detailed to determine how yellow fever was spread, examined existing theories and was particularly impressed by Finlay's 1881 mosquito hypothesis. This, coupled with Carter's observations made in Mississippi in 1898, suggesting an incubation from first infecting case to later secondary cases of from two to three weeks, influenced Walter Reed and his associates to explore mosquito vectors. Their deductions were correct, and they made a convincing demonstration of yellow fever transmission to human volunteers by the bite of infected *Aedes aegypti* [18]. The control of the demonstrated vector brought yellow fever under control in the major port cities of the Old World and the New World. It was thought, in the early decades of the twentieth century, that the disease could be vanquished. However, some unexplained outbreaks of yellow fever continued to be seen, particularly in the hinterlands of South America. Soper and co-workers published a paper [19] which caused anguish. They described yellow fever in the State of Espirito Santo, Brazil, in the absence of *Aedes aegypti*. Mosquitoes of the genus *Haemagogus*, a genus quite closely related to *Aedes*, were shown to be the vectors for a jungle (or sylvan, or forest) cycle of yellow fever, in which forest primates served as the vertebrate host, in places where man was only an occasional invader and, in effect, an accidental host, not responsible for long-term maintenance of the disease. Bugher et al. [20] describe the observations of Boshell Manrique that mosquitoes of this genus appeared suddenly at ground level when trees were being felled. This observation led to numerous later studies on the species composition and vertical distribution of mosquito populations (and populations of other biting arthropods) and carried disease epidemiology into the forest canopy. Mosquitoes of several other genera in the New World were shown to be possible vectors. In the Old World, *Aedes* of several species were shown to maintain a cycle of jungle yellow fever, and mosquitoes of several other genera were shown to be secondarily involved. Virus was even isolated once from a *Phlebotomus* fly.

Thoughts of overall control were banished, but also, it was apparent that the protection of major population centers remained possible through urban *A. aegypti* control programs.

Another control methodology was introduced in the mid-thirties with the development of yellow fever vaccines. French workers developed a mouse brain vaccine from the French neurotropic strain of virus, given by scarification. Successive modifications were made, with the vaccine of Peltier and Durieux [21] being used for immunization of millions in the French West African colonies. The vaccine, often administered with smallpox vaccine, induced a high degree of immunity, but there were also vaccine reactions, some of them, particularly in small children, of encephalitic type. This vaccine has been almost entirely supplanted by the attenuated 17D vaccine, developed by Theiler and Smith [22], and now in use worldwide; it is produced in embryonated chicken eggs. Reactions to the 17D vaccine are uncommon. Immunity induced is very long-lasting, quite possibly lifelong.

Each of these control options is flawed. The early techniques developed for control of the vector were refined to the point where Soper et al. [23] in a campaign backed by the Brazilian government and the Rockefeller Foundation, announced the eradication of *Aedes aegypti* from Brazil. The massive operation was successful, in the era before DDT was known. When the new insecticides, heralded by DDT, did arrive it appeared that Soper's painstaking strategy for mosquito control could be extended and simplified, and at least in the New World the possibility of hemispheric eradication was entertained. *Aedes aegypti* was eradicated from many Central and South American countries. Nature again showed her colors, and gloom succeeded happiness when it was shown, in the late 1950s, that the mosquitoes were developing a resistance to DDT and also to other insecticides. The mosquito reinvaded many areas where it had been eradicated, and, following its reappearance and multiplication, dengue epidemics (also *Aedes aegypti* transmitted) are being seen annually in the West Indies and northern South America. The risk of reappearance of urban yellow fever is obvious. This brings us to the second point, the vaccine, which can be afforded and which can protect any person or population immunized. An immunization program reaching all the population at risk is difficult to conduct. The risk perceived does not appear commensurate with the effect involved, and in very few places are continuing effective vaccination programs in operation today. The problem for the individual, be this individual an international traveler or a concerned individual living in a yellow fever endemic locale, is not a difficult one. But for the populations in the hinterlands of Africa or the Americas, it remains a large problem. The vaccine is not very heat stable, and requires a "cold chain" in order to guarantee conformity of the vaccine being administered with International Regulations. The development of the air jet vaccination apparatus accelerates a mass vaccination campaign greatly. In the event of an outbreak in a major city, today's approach is to start an immunization program immediately, and to do a thorough mosquito cleanup, treating and if possible destroying all *Aedes* breeding places. An immediate campaign of adulticiding, hoping to kill any infected mosquitoes, as well as reducing the numbers of mosquitoes, is mounted, with insecticide fogs laid down by aircraft, and by specially adapted ground-based spraying and fogging vehicles and portable sprayers. This approach is practical and assures prompt epidemic control. However, if diagnosis of the first case(s) is not made early, an urban epidemic could well be in the second or third wave of transmission before control gets started, and there might easily be several hundred individuals infected, with many deaths.

The unfolding of the jungle yellow fever story, and the implication of primates of both Old World and New World in a cycle of virus transmission high in the canopy of tropical rain forests seemed like too simplistic a story to satisfy the critical investigator. Bugher, in the chapter entitled "The Mammalian Host in Yellow Fever"

in Strode [1], reports on extensive exploratory work in Africa and tropical America, particularly Colombia and Brazil, carried out through the 1930s. Investigations were carried out on several orders of mammals and also on birds and poikilothermic vertebrates. These investigations dealt with susceptibility, with presence of immunity in native animals, and with interaction of such animals with possible or known vectors, including vector distribution, activities, and behavior, both at ground level and in forest canopy. There is an excellent summary of findings through 1950, and these studies have been supplemented by several later studies, including those of Henderson et al. [24] in East Africa and Gorgas Memorial Laboratory [25] work with sloths in Panama. Charles Anderson worked on animals in Colombia and Trinidad. The demonstration by Beaty and Thompson et al. [26] of the association of La Crosse virus (a member of the California group of Bunyaviridae) with *Aedes triseriatus*, a treehole and discarded automobile tire breeding mosquito, the common chipmunk, and a deadly encephalitis infection in man, in Wisconsin is a dramatic example of virus persistence in a limited focus. Thompson and Beaty have also demonstrated [27] venereal transmission, or horizontal transmission, of virus from a transovarially infected male to an uninfected female.

Attention has been focused on the monkey-mosquito-monkey cycle, and on other possible cycles, in hopes of gaining a clear understanding of puzzling epidemiological aspects of yellow fever virus maintenance in natural surroundings. In several of the known immense virus endemic regions in Africa and South America, epidemic outbreaks have occurred after long intervals of apparent freedom from virus activity. Only a very few study spots exist in the regions in question. In such centers, it has not been possible to find the virus in interepidemic intervals, even following careful search among the endemic vertebrate species, and the endemic vectors and possible vectors. In some of the regions, such as Trinidad, it has been thought [28] that the existing populations of monkeys are not numerous enough to maintain the virus in silent fashion over a period of several years. Yet yellow fever outbreaks have occurred on the island in 1914, possibly in the mid-1930s (never verified), and verified in 1954, 1959, and 1979.

Loring Whitman, in the chapter "The Arthropod Vectors of Yellow Fever" in Strode's *Yellow Fever* [1], gives a thorough exposition of knowledge up to 1950. A chapter subheading is: "Possibility of Virus Passage from Mosquito to Mosquito." This is a subset of the epidemiological quest, and the attempt to explain long-continuing existence of the virus in the face of hostile Nature. If the human population is not a permanent reservoir of the virus, if there are questions raised about the ability of monkey populations to serve as permanent reservoirs, and if no known small animals fill the bill, possibly a permanent reservoir exists in certain mosquito species. Marchoux and Simond [29] claimed to have transmitted yellow fever to a human volunteer (those were heroic days of epidemiology) by bite of *Aedes aegypti* reared from an egg of an *Aedes* which had been permitted to bite on a yellow fever patient. Unhappily, the data leave doubt as to the validity of the observation. A number of later studies failed to confirm the hypothesis of transovarial transmission of virus.

Rosen et al. [30] succeeded in demonstrating transovarial passage of the viruses of Japanese encephalitis and of dengue and this work was soon followed by demonstration of transovarial passage of the yellow fever virus in *Aedes aegypti* by Beaty, Tesh, and Aitken [31]. These breakthroughs were made possible through use of newly developed techniques of immunofluorescence and "tagged" antibody which permitted rapid examination of hundreds of thousands of individual mosquitoes.

The phenomenon demonstrated for yellow fever is a low-level phenomenon, successful transovarial passage being at about a 1 percent level. Studies are being undertaken involving several strains of *A. aegypti*, other vectors, and other strains of virus in order to know how far one dares to extrapolate from what has been observed. Concurrent with these laboratory studies there are field observations from Africa providing new insights and highlighting new avenues for exploration. Cornet et al. [5] report Institut Pasteur field studies in the vicinity of Kedougou in southeast Senegal. They have made numerous isolations of yellow fever from mosquitoes of the *Aedes taylori-furcifer* complex. Isolations have been made from female and male mosquitoes. There has been no overt evidence of yellow fever activity in the region, as evidenced by recognizable cases of illness in man or monkeys. This focus remained active for two years, after which the virus has disappeared. The mosquito complex is under intensive study and it appears that it will be possible to identify the two *Aedes* species in field-collected material, and to subject each species to detailed studies of susceptibility, life cycle, and behavior, including feeding preferences. Germain et al. [32] at the Institut Pasteur in Bangui, Central African Republic, report the isolation of yellow fever virus from a tick, *Amblyomma variegatum*, taken from cattle, and has succeeded in transmitting the virus to a susceptible monkey by bite of offspring of an infected tick. These findings—the demonstration of transovarial passage of virus, the finding of infected male mosquitoes in the field (implying transovarial passage and not excluding venereal passage of virus), and the findings of infected ticks and infected offspring of infected ticks, capable of transmitting virus by bite—have provided information of fundamental importance. We do not know how to evaluate these findings in relation to the epidemiology of yellow fever. Will they prove to be of major or minor importance?

Seroepidemiological studies on a large scale, to determine the worldwide distribution of yellow fever, were possible after Theiler's [33] demonstration of the susceptibility of the Swiss white mouse to yellow fever virus. The first surveys, spanning the world, were carried out with a mouse neutralization test wherein an immune serum or a serum to be tested was inoculated intraperitoneally into mice, followed by intraperitoneal inoculation of a serum containing a measured amount of virus. The findings delimited the range of yellow fever to Africa south of the Sahara and north of the Tropic of Capricorn, and to the equatorial and subsequatorial regions of South and Central America. Extremely few "false" reactions were observed in test sera from regions known to be free of yellow fever. The neutralization test used was a very crude one, or, in other terms, a test very specific for yellow fever, and not influenced by the antibodies to other flaviviruses which might be present. Yellow fever is a flavivirus, a group of viruses liberally distributed around the world, and containing such agents as the dengues, St. Louis encephalitis virus, Japanese encephalitis virus, and many others. Modernized neutralization tests are of several types, including intracerebral inoculation of the virus under test, in adult, weanling, or infant mice, and various modifications of cell culture tests and the recently developed ELISA test (enzyme-linked immunosorbent assay). These tests are plagued with the cross-reactive antibodies common to the flavivirus group. Had the original worldwide surveys been attempted with these more sensitive tests, the pattern of yellow fever immunity would have been much obscured. In modern immunological studies, even when quite specifically narrowed down, as can be done, for example, with a specifically designed ELISA test, one cannot differentiate between immunity induced by an infection with a "wild" strain of yellow fever, as encountered in an endemic region or during an epidemic, and the immunity induced by an inoculation

of the 17D vaccine. Studies in yellow fever endemic regions to determine the recent history of yellow fever are much hampered by antibodies present in people already vaccinated. One is forced to locate and test remotely situated tribal peoples who have not been vaccinated, or to limit a study to young children, born after the date of the last vaccination campaign. Clarke [34] showed that by a technique of differential absorption of yellow fever antibodies from a potent immune serum, the yellow fever virus in unadapted form could be distinguished from the 17D vaccine virus. Indeed she showed a subtle difference between a virus strain from South America and one from Africa. The test was a laborious one, involving careful mixing of serum and virus, high-speed centrifuging of the mixture, and then search in the hemagglutination inhibition test for an antibody moiety not removed by the absorption and centrifugation procedure. She demonstrated such a moiety in 17D immune serum absorbed by a "wild" virus strain, such as the Asibi strain from West Africa. In an Asibi immune serum absorbed by the 17D virus antigen, all antibody was removed. Therefore, the 17D virus has an additional antigen component not present in the parent (Asibi) virus strain. Instead of its being a selected clone from a polyvalent "wild" virus, it appears that it is a true mutant. Numerous attempts have been made to reproduce this mutation event, scrupulously following the original protocols of Theiler and Smith, and following new protocols aimed at induction and selection of mutations. The event has never been repeated. The rapidly evolving modern field of virus particle isolation and breakdown and separation of components, coupled with bioengineering, makes it possible to consider the isolation of the extra component of the 17D virus particle, and to multiply this antigenic fraction, to be used in highly specific immunological tests. Such a test would be a boon to yellow fever epidemiology.

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