Jungle Yellow Fever

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Jungle yellow fever is the disease in man resulting from the forest cycle of the virus for which the presence of man is not essential. Basically, one is concerned only with the human manifestations, but since it is the epidemiological mechanism rather than the clinical aspect that is distinctive, the discussion here will deal with the characteristics of the virus cycle rather than the clinical picture.

The term “Jungle Yellow Fever” may be blamed on Dr. Fred Soper or on Dr. Jorge Boshell Manrique or on both together. Dr. Soper used it in discussing Dr. Boshell’s work at a conference in Bogotá in 1935. Since then many persons have objected to it for numerous and good reasons but nobody has produced a more satisfactory term. The word “jungle” suggests a tropical rain forest to most of us without specifying the location or the composition of the flora and fauna. And yet, notwithstanding its great variation, we at once recognize such a forest as being quite different from any in the northern regions.

Jungle yellow fever is associated with such tropical forests and the virus cycle may assume as many different variations as do the forests themselves; but withal there is a certain consistency and harmony among all of these situations. One may speak of an epidemiological (despite the etymological objections which may be raised, I prefer to extend the term “epidemic” to the forest animal community, including man, rather than to introduce the clumsy word “epizoötic”) pattern which holds good generally but the elements of this pattern may differ substantially from one geographic region to another and within the same area at different periods of time.

The first definite association of yellow fever with the forest of which I have knowledge was by Roberto Franco and his associates as a result of their studies at Muzo, Colombia, in 1907 and 1908. They clearly differentiated malaria, relapsing fever and yellow fever; and they attributed the infection to the attacks by silvan mosquitoes on individuals who had penetrated the forest remote from the town. As is not infrequent in scientific matters, Dr.
Franco had outstepped the pace of history and it was not until nearly a quarter of a century later that the accuracy and significance of his observations became generally apparent.

On the basis of Thomas' work at Manáos in 1905, Sir Patrick Manson raised the question of the importance of forest animals, especially monkeys, in yellow fever. He suggested that if the virus could be carried by mosquitoes from man to animals, then it also could be carried in the reverse direction.

Balfour, impressed by the evidence that red howler monkeys had been involved in epidemics of yellow fever in Trinidad, suggested to the British Colonial Office that the possibility of monkeys acting as reservoirs of yellow fever virus would justify a careful study of the monkeys of West Africa. The onset of World War I prevented this plan from being put into operation and many years were to pass before any adequate studies were undertaken. Fundamentally, until the virus was available in a laboratory animal, little definitive work in this area was possible.

The intervening years saw spectacular success in the control and eradication of yellow fever in many regions based on the man-Aedes aegypti-man cycle. The great majority of workers were convinced that this abundantly proved mechanism was the only one in existence. It required the rural epidemic of 1932 in Espirito Santo, Brazil, in the absence of Aedes aegypti, to destroy the complacency and to open an exciting new period in our experience with this disease. It is probably true that had it not been for the work of the previous years which had led to unequivocal methods of diagnosis, this outbreak would have passed unrecognized as to its true nature.

**Principles and Mechanisms**

It is immediately apparent that several basic conditions must coexist if a natural cycle of virus transmission is to be maintained. These are:

1. The animal in question must be susceptible to the virus. When a small quantity of the virus is introduced into the animal, multiplication of the virus must result; that is, a true infection must occur.

2. Virus in an infected animal must be transferable to other animals, either directly or by mediation of a vector such as an arthropod.

3. In the case of a mediating organism or vector, the circumstances must be such as to permit the transference of virus from the animal to the vector. This is equivalent to stating that host and vector must share the same habitat for at least a portion of the time.

4. The vector must be able to transfer the virus to other susceptible animals of the same or other species with sufficient frequency to permit continuity of the cycle.
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Until the present time, in the vast areas of South America and Africa where the virus is maintained endemically without the required participation by man, the arthropod is a mosquito and the animal is a mammal, usually a primate (other than man), but in South America there may be the minor intervention of several species of marsupialia and possibly some species of rodentia. In Africa, the forest cycle appears to be exclusively related to the monkeys although it must be conceded that the entire subject of the animal host in Africa has as yet been only superficially explored.

The mosquito vector in South America appears to be predominantly of the genus Haemagogus, especially H. spegazzinii falco, with minor contributions from Aedes, notably A. leucocelaenus.

In Africa, the proved forest vector is Aedes africanus in the area of Uganda. No virus has been isolated from forest mosquitoes in West Africa but the evidence, as far as it goes, presents nothing to contradict the thesis that A. africanus is the chief vector.

In all of these endemic regions, the chief mosquito vector is distinctly arboreal in habit, the greater portion of the biting population being in the foliage canopy. This would appear to relate to the more arboreal animals as the most important animal hosts.

Little is known of the population densities and life span of the important mosquitoes. For persistence of virus, the mosquitoes must be capable of living through the dry season, since none of the animal species exhibit circulating virus for more than a few days. There is presumably some level of population density below which virus propagation will not be maintained. Clearly, the insects which have had infectious blood meals must have a life span sufficient to encompass the extrinsic incubation period and give time for the delivery of a few bites after becoming infective. It is perfectly possible to have a very dense mosquito population but with a life span so short that it cannot serve to transfer virus from animal to animal.

There must be some relationship between the number of susceptible animals, the virus levels reached in the infected ones and the density of the vector mosquitoes. Small probabilities, leading to transmission failures in the laboratory, may nevertheless be adequate for continuous propagation of the virus in nature where the animals concerned may be counted by the thousands and the mosquitoes by millions. An animal with a low virus titer may have but a small chance of infecting a single mosquito; but if several thousand feed on him during the days of virus circulation even a small probability may result in there being a few capable of transmission. With a highly efficient vector, the probability of establishing another active animal infection is essentially the chance that an infectious mosquito encounter a non-immune animal in the course of feeding upon several. With an abundant animal population of modest proportion of immunity, this chance may be quite high.
There is no demonstrable threshold of infectivity so that the entire mechanism may be regarded as a probability system in which the value is never zero as long as the three components of susceptible animal host, mosquito vector and virus are present but whose value rises with the increase in density of any one of the components and becomes maximal when all three reach their highest values simultaneously or nearly so. The fact that we cannot put numerical values to these population statements indicates how much is still unknown in the epidemiology of jungle yellow fever.

The spread of virus in the forest will be compounded of the movements of host and vector. Most forest animals, especially primates, have a limited range. It is likely that wind transport of infected mosquitoes is a most important factor and there is some evidence suggesting this, but much more study is necessary.

South America

The clinical yellow fever seen in South and Central America is almost in toto jungle yellow fever. *Aedes aegypti* transmission has been infrequent for many years. The opportunity to study the circumstances under which man becomes infected has been vastly better in South America than in Africa where the occasionally occurring forest infection is lost in the sea of *A. aegypti* transmitted village disease. It has long been evident that it is the people who disturb the forest during the day who fall ill of yellow fever. The woodcutters, those who cut roads and trails through the forest, the hunters, and those who clear the land for cultivation constitute the population among whom most of the cases of jungle yellow fever occur. These circumstances are made almost inevitable by the biology of the chief vector, *Haemagogus spegazzinii*. The mosquito is markedly phototropic and has its peak biting cycle in the midportion of the day. Any disturbance of the forest canopy, especially if accompanied by an increase in light, results in a vigorous attack upon any nearby warm-blooded animal. Since the usual cause of such a disturbance is likely to be man, the connection is obvious.

The mammalian host appears to be somewhat more complicated. There are great differences in the virulence of the virus for the numerous species of primates, but they are all susceptible and there are probably none that may not, under special conditions, serve as the intermediate host. It does not appear that the same species will necessarily have the same importance in different regions. In general, a primate population that has negligible mortality seems more favorable for protracted endemcity; while one that tends to exhibit high mortality and high titers of circulating virus tends to a fulminating type of outbreak which may effectively depopulate the area of the species in question.

In addition to the role of monkeys in the forest cycle, there is strong evidence that in many regions marsupials may assume the mammalian part.
Some of the species of marsupialia are quite susceptible to infection and may constitute the preponderance of the total number of infected animals. In special regions, such as the Municipio of Muzo in Boyaca, Colombia, monkeys appear to be entirely absent and in similar regions of the western slope of the Magdalena valley in Antioquia there is likewise an absence or great scarcity of any primate save man. These conditions have obtained for at least 50 years in these localities and one is forced to the conclusion that if any primate has participated in the epidemiology of yellow fever in recent times, it has been man himself. Otherwise, the zoological and immunological evidence points to marsupials such as Metachirus and Caluromys as the mammals contributing chiefly to the mammalian portion of the virus cycle. The abundance of the marsupial population together with its rapid turnover would appear to compensate for the generally higher susceptibility of the primates.

Monkey yellow fever has been demonstrated in regions devoid of human habitation; forest epidemics have occurred in regions of mixed monkey and marsupial population with some intermingling of people; endemic yellow fever has long been known in at least one area rich in marsupials with considerable human infiltration into the forest.

If one examines only single, small areas, the yellow fever virus appears rather suddenly, reaches a maximum of animal involvement in a few weeks or months and then disappears, leaving a partially immunized animal population. Several years may pass before it is again demonstrable. Such apparent discontinuity has given rise to considerable speculation that in the interval the virus must have persisted in some as yet unrecognized silent form.

When, however, careful scrutiny is given to a large region, one invariably finds that there is virus activity at some place in the area all of the time. The active front moves about, dependent upon the concordance of the necessary ecological factors such as a sufficient density of non-immune susceptible animals, an adequate population of the suitable mosquito, etc. Yellow fever, in the forest cycle of the virus, is thus endemic in the large sense but intermittent or cyclic with respect to particular regions.

The human infections, being incidental to this fundamental forest epidemiology, reflect the existing virus activity to the extent that there is human contact with the forest. A further complication is concerned with the means whereby the existence of human infections is recognized. Without a diagnostic and reporting system, there may actually be an astounding amount of severe but statistically unrecognized yellow fever. There is no one who can speak with greater feeling on this particular subject than Dr. Soper.

Africa

When one considers the problem of jungle yellow fever in Africa, a number of strikingly different conditions become evident. In the first place,
while there are great areas of South America where *Aedes aegypti* transmission is non-existent or insignificant, there is no portion of the endemic region of Central Africa where this mosquito is not to be found in the villages. Furthermore, *A. aegypti* transmission of the virus from man to man is actually very common. There is immunological evidence that during the last war there were about 100,000 new yellow fever infections each year in Southern Nigeria alone, almost all of it unrecognized at the time. For reasons to be explained later, it appears that the probability of an individual acquiring the infection in the forest is appreciably less than in South America. Very few of the total number of recognizable cases of yellow fever are actually of jungle origin and in the presence of the vastly greater number of *A. aegypti* transmissions, there is almost no chance, especially in West Africa, of clearly associating a given case with the forest. Among many hundreds of cases of yellow fever in Nigeria and the Gold Coast, I do not know of a single one that was not obviously of the classical urban type.

The forest cycle of the virus in all of Central Africa appears to be associated with *Aedes africanus*. Other culicines, such as *A. luteocephalus* may play an active role in some situations but in general these must be regarded as secondary. In contrast to the daytime biting habit of *Haemagogus* in South America, *A. africanus* is a crepuscular biter with its main biting peak just after sundown and a smaller phase of activity before sunrise. At dusk, the people have left the forest for their clearings and villages into which this species does not penetrate. At this time, however, the monkeys have repaired to their sleeping trees and have become quiet for the night, making excellent victims for the canopy-loving *A. africanus*. The association of the monkeys with this mosquito is thus vastly more intimate than it is with man.

The weight of evidence in East Africa is that the transfer of virus from monkey to man is mediated by *A. simpsoni* which breeds especially in banana plantings and will not only penetrate for a short distance into the neighboring forest but will enter the houses in the clearings. Certain species of monkeys are noted for their habitual raiding of the plantings and it is this situation that appears to result in the delivery of virus to man. *A. simpsoni* transmission of yellow fever in Uganda has been recognized and is probably reasonably frequent.

In contrast, *A. simpsoni* is a difficult mosquito to find in West Africa and although monkey yellow fever is widespread, the transfer to man has apparently a lower probability and true cases of jungle yellow fever are probably far less frequent than in Uganda. As banana cultivation increases in the Cameroons and Nigeria, it is possible that the yellow fever problem will become more difficult with increasing numbers of *A. simpsoni*.

The animal studies, so far as they have gone in Africa, have failed to demonstrate any participation in the forest cycles by animals other than
primates. There is a very rich fauna of this Order, varying from the tiny *Galago demidovii* to the *Gorilla*. Most of the species are diurnal but many of the lemurs are almost strictly nocturnal. There are numerous additional factors which determine whether a given species will participate in the virus cycle. The *Galago senegalensis*, for example, is fully susceptible to infection but it inhabits the savanna forest which is unsuitable for *A. africanus*; consequently, this primate plays no part in the cycle in any of the areas studied.

In other regions, such as the Sudan, epidemic yellow fever has occurred under conditions markedly different from those associated with the rain forests. Here the circumstances appear to resemble more those of rural yellow fever in Brazil and constitute a special situation by no means fully understood.

**Summary**

We have come to accept as well-established a fundamental forest epidemiology which, although with important differences, applies generally to both South America and Africa. Is this all? Possibly not. The history of yellow fever is one of the best examples of the dangers of being completely satisfied with an explanation that accounts for all of the known facts. It is sound science not to elaborate a theory far beyond the data; it is also important not to permit a satisfactory rationalization to stand in the way of further explorations. It is quite possible that beyond the natural cycles of the yellow fever virus which we now recognize, there are others for which at the moment we have no reliable evidence at all. Much remains to be done, especially with the dynamics of the mosquito vectors, before we have adequate understanding of the mechanisms involved in the spread of the virus through the forest and its stubborn persistence in some areas in contrast to its evanescent character in others.