Yellow fever can first be identified with any degree of certainty in the New World in connexion with an outbreak of 1646 in Guadaloupe and other islands of the French Antilles, and an outbreak in 1648 in Yucatan. This antedates any recognizable disease in Africa by a century. Carter, (1931) writes in detail of his searches for evidence of pre-Colombian existence of the disease in the New World. No convincing accounts exist.

Scott (1939) still did not wish to come to final grips with the question of whether YF was of Old World or New World origin. He provides a very useful listing of YF outbreaks up to 1936, both in Africa and the New World.

With the unfolding of the story of jungle yellow fever in the Americas dramatically presented in Soper's (1970) book, followed by recognition of a corresponding, although far from identical cycle in Africa, from the mid-1930's on, the question of continent of origin of YF still remained unanswered.

Clarke (1960) produced evidence that YF strains originating in Africa had an antigenic component absent from the South American strain studied. She acknowledges the limitations of the study, namely the small number of African (3) and American (1) strains investigated. An extension of this study at a later date provided evidence that an Ethiopian strain was not identical with a West African strain. Further extension of these investigations of virus relationship by antibody absorption, using several African virus strains and several New World strains is needed.

The recognition of the jungle YF cycle in the Americas led to investigations of susceptibility of New World primate populations. Early investigations have been reviewed in the basic review and reference source "Yellow Fever" (Strode, 1951). The position as outlined there has not changed remarkably. A number of species of marmosets were tested for susceptibility and all species were susceptible, the infections often being fatal. Virus isolations were made from Callithrix penicillata captured during the course of a yellow fever outbreak in the Ilheus region of Brazil in 1944. In studies of susceptibility, it was shown for two species that mortality was considerably higher following inoculation with South American strains of virus than following inoculation with African strains.

The howler monkeys (Alouatta), distributed widely in several species from Argentina to southern Mexico are very susceptible, infection often being fatal. It has been possible in
certain epidemics, (Central America in the 1950's for example) to follow the geographical progress of the epidemic by finding dead monkeys. Following an epidemic wave, howler monkey populations may be markedly reduced. Nonetheless, immune animals can be found, and immunological studies of the endemic howler monkey population of a region are useful in detecting activity of the disease in the absence of overt declarations of disease presence. It has been shown that virus can be readily recovered from the liver or serum of monkeys found dead in the forest, even when considerable autolysis of tissues has occurred. This observation presumably might be extended to monkeys of other species. Howler monkeys are essentially animals of deep forest, and if space considerations are not pressing, apparently prefer to remain well separated from human habitation.

The saimiri monkeys of northern South America are also susceptible to YF, with mortality rates approaching 50%.

The night monkeys (Actes trivirgatus) of the Amazon, Orinoco and Magdalena basins also are readily infected with YF, and have a high mortality rate. These monkeys are commoner than was earlier suspected (although recent demonstrations of suitability as a host for human malaria parasites has made them in demand, a factor which may affect population densities).

The spider monkeys (Ateles) are susceptible to YF, responding with high mortality. Woolly monkeys (Lagothrix) could be infected but limited observations indicate that mortality rates may not be high.

Capuchin monkeys (Cebus sp.) can be infected readily with YF, circulate virus and develop immunity, but mortality rates are low.

The dynamics of the maintenance of YF in the vast endemic areas of South America are far from clearly understood today. In a broad general statement, it can be safely said that YF, at any given point in time, is on the move in an epidemic or sub-epidemic form, in various localities. Just what particular localities are affected at any given point in time it is not possible to say.

To refine the question further, can we with certainty state that any given region which has been known to have had a jungle YF outbreak in times past does not have residual endemicity at this moment? Again one has to define "region" more precisely. If we reduce "region" to a 50 square mile area, we can with some confidence say (for Trinidad for example) that since 1959, the date of the last recognized outbreak, it has not been possible to detect any evidence of endemic disease. Studies of that region are more thorough than for any other similar or much larger regions. Nonetheless, they are far from adequate. A continuing degree of vigilance is maintained, but not sustained at a high level continuously. Investigators in Panama, covering all of Central America north of Darien, feel reasonably certain that following the epidemic YF sweep of the 1950's, there is now no endemic disease in the region.

The Belem Virus Laboratory, the sole adequately equipped listening post for the whole Amazon region, has YF surveillance as a natural component of its more general arbovirus programme. Over the past 20 years, they have uncovered seven episodes of yellow fever activity in the region in close proximity to the laboratory. It is certain that most of these episodes would have gone unrecognized had the laboratory not been there. What may be going on the remainder of the Amazon territory cannot be even guessed at.

In any discussion of endemicity, the possible role of non-primate vertebrates comes up for discussion. There have been attempts to evaluate receptiveness of various marsupials, rodents, edentates and bats to infection and it has been established that various mammals can be infected, can circulate virus and can develop detectable antibodies. Serological studies of mammal populations however, have not yielded information which would lead one to conclude, or even to suspect, that one or another of the species studied is involved in an endemic cycle on other than a casual, even accidental basis.
Birds and poikilothermic vertebrates have not been overlooked in the quest for a non-primate endemic cycle. It has not been possible to develop the concept beyond the point of low-level, short-term viremias and occasional neutralization test positives, difficult to evaluate.

The vectors of jungle YF are dealt with at length in Strode's "Yellow Fever". Mosquitos of the genus Haemagogus are without doubt the primary important vectors. Mosquitos of other genera (Aedes, Sabethes) have been infected experimentally and can transmit, and infected mosquitos have been captured in nature. There is no evidence however that non-Haemagogus mosquitos are involved in other than a secondary fashion.

In the 1954 Trinidad outbreak, it was possible to locate a specific tree harbouring a dying Alouatta monkey. Captures of Haemagogus mosquitos positive for YF virus were made for more than a week following this event, from the canopy of this very tree. A study of Alouatta monkeys carried out in Trinidad in the 1954 period indicated a probability greater than chance, that a given monkey band would be composed of monkeys all YF negative, at one extreme, or with a high proportion of positives, on the other.

These limited facts lend some support to a concept that in the jungle, the YF virus may be continually on the move, and that one might conceive of an endemic focus as a focus of several hundred, or even several thousand square miles, with virus somewhere in the area, always, but with no possibility short of an extremely detailed study, of knowing exactly where. An infected monkey in a band could infect many mosquitos in a given tree. This tree would remain a danger spot for several weeks. If invaded by monkeys of another band (if the tree happened to be in a boundary zone where band-territories overlap) while a danger spot, infection would be passed on to the next band. Several new infective foci might then be established a few days later and several miles distant. Although several new danger spots might be established, successful involvement of another monkey band (with susceptible monkeys therein) would only be needed for one of the danger spots for the virus to be assured of its continuing maintenance in the region. The territorial behaviour of monkey bands introduces an important factor to be considered.

Obviously, when an intense epidemic such as the Central American one occurs, the virus is more than ordinarily successful in its movement (into populations presumably completely susceptible), and virtually all monkeys are involved.

Movement of virus from the monkey - Haemagogus cycle into humans is an accidental phenomenon, secondary to human invasion of the infected focus. In instances where non-immunized labourers are working in the jungle there may be sharp outbreaks. It is important to remember in connexion with human-Haemagogus inter-action, that the Haemagogus mosquitos are not restricted to canopy, but are often found biting at ground level, in sunny clearings, at roadsides, etc., and have also been observed biting within houses (although they should not be considered as house-haunting mosquitos).

The natural history of urban yellow fever in the Americas can be restricted to Aedes aegypti-human cycle. For urban areas, where Aedes aegypti has been eradicated, there is no evidence that any other mosquito, even species shown in experimental studies to be capable of transmitting virus, can successfully function to maintain endemic or epidemic YF. Much remains unknown about the urban yellow fever epidemic model. Recognizable variables of mosquito density, proportion of susceptibles in the human population, and longevity of mosquitos under the influence of local climatic factors and less understood variables as the non-YF group B immune status of a given population have to be considered. It is not known, for example, under ideal circumstances of a completely susceptible population without other group B antibodies, what density of Aedes aegypti might be required to produce an epidemic. It has also been hypothesized that group B immunity (dengue has been particularly suspect in this connexion) might serve to modify the course of YF in the individual, shortening the
viremic phase and depressing the virus titre levels attained in the individual. Such a pattern has been shown in animal models, and if applicable to humans, would be a considerable dampening influence.

Continuing YF activity in the tropical and subtropical jungle areas of the Americas can be expected. Human involvement can be lessened by effective YF vaccination programmes. Aedes aegypti had been eradicated or reduced to levels presumably below those necessary to produce urban YF outbreaks in many of the Central and South American countries and Caribbean islands. However, in the past two decades, insecticide resistant Aedes have become established in many sites. Recent dengue outbreaks in circum-Caribbean and northern South American countries have provided evidence that Aedes aegypti densities adequate to cause an epidemic now exist in a number of localities. This is a very dangerous situation. Chance introduction of virus may lead to an explosive outbreak, if the situation is not recognized for what it is early. Immunization of populations in urban centres where Aedes aegypti is known to exist can provide adequate control. It appears unlikely that, in the absence of recognized disease, such immunization will be carried out. Sporadic mass vaccination programmes in absence of recognizable disease may indeed upon occasion be organized by a conscientious health department, but it is unlikely that continuing programmes of vaccination of new susceptibles will be maintained.

Aedes aegypti control or eradication is of course a prime consideration for control of urban yellow fever. The Pan American Health Organization has been much interested in this problem and has had recent conferences to determine feasibility. Certain of the countries involved have achieved eradication but are plagued by reintroduction from neighbouring countries. Certain other countries which had had programmes aimed at eradication, and which had at least arrived at a level of a high degree of control, have in recent years relaxed control efforts. The eradication programme on which the United States of America had embarked is now non-operative. The problem in the administrative area is whether an effective control programme in any particular country is likely to be continued at an effective level indefinitely.

The question of whether YF virus, in rapid passage from human to Aedes aegypti to human in an urban outbreak may undergo an enhancement of virulence for the human host is one which gets raised periodically. It is impossible to test the hypothesis in the human host under conditions of a controlled experiment. It is possible, although it has not been done, that markers for virulence might be found under conditions of laboratory maintenance of virus, in cell culture systems or in vivo. The difficulty of relating any such markers back to the human host will remain. Differences in virulence of field isolated strains, of virus, with low or no mouse passage, when tested in Rhesus monkeys, are already known. Again relevance to human disease is not clear.

A further difficulty lies in recognition of sporadic yellow fever cases, which may have few of the characteristics of the classical disease picture. A single sporadic case unrecognized may be all that is needed to give rise to an epidemic. The epidemic itself, while gathering headway, may not be recognized as yellow fever until in the second or third wave of transmission. The ideal solution lies in the maintenance of a series of listening posts, able to diagnose yellow fever quickly and correctly, by application of appropriate virological techniques. Two such posts, the Trinidad laboratory and the Belém laboratory, face the very real threat of loss of such competency through lack of adequate continuing financing.
REFERENCES

1. Carter, H. R. (1931) Yellow fever: an epidemiological and historical study of its place of origin. Williams & Wilkins Company, pp. i-xii, 1-308

