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# The Newer Epidemiology of Yellow Fever*

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THE extent to which present beliefs regarding the epidemiology of yellow fever differ from those of just a few years ago is not generally known outside of the small group of workers actively engaged in the study and control of this disease. It must come as a great surprise to the majority of the members of the American Public Health Association, meeting here in New Orleans, one of the cities of the United States previously most exposed to the ravages of yellow fever, but since 1905 free of this scourge of the American tropics, to learn that the epidemiology of yellow fever is still a sufficiently important problem to merit a place on a program devoted to public health problems of immediate interest to health workers in the United States. Your surprise, however great, cannot equal the reluctance with which those engaged in the study and control of yellow fever in South America have relinquished their faith in the simple man-*Aëdes aegypti*-man epidemiology, consecrated by the almost miraculous results obtained in the West Indies and in North, Central, and South America during a full quarter of a century by a brilliant coterie of workers drawing their inspiration from the early work of Gorgas in Havana and of Oswaldo Cruz in Rio de Janeiro.

The period from the first observation of yellow fever to the demonstration in 1900[1] that its virus could be transmitted from man to man by the mosquito, *Aëdes (Stegomyia) aegypti*, may well be called the Dark Age in the history of the disease. More or less constant endemicity existed in many of the ports of tropical America, and the disease made not infrequent summer excursions into both the North and South Temperate Zones. Quarantine and other restrictive measures were common, and trade with the American tropics was difficult and costly.

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† The studies and observations on which this report is based were made under the auspices of the International Health Division of The Rockefeller Foundation in coöperation with the Governments of Brazil, Bolivia, Paraguay, Peru, Ecuador, Colombia, and Venezuela. The report covers the work of numerous colleagues of the staff of the International Health Division and of the staffs of the Coöperative Yellow Fever Services in the respective countries.

The discovery of the urban, domestic vector of yellow fever was followed by a Golden Age of magnificent achievement and glorious dreams based on that achievement. During this Golden Age which covers the period 1901 to 1925, anti-mosquito services organized in many of the most notorious key-centers of infection on the continent resulted in the rapid disappearance of yellow fever from the morbidity and mortality statistics not only of the centers where such services were installed but also from those of large tributary regions. To the sanitation of Havana and Panama was attributed the great reduction in the incidence of yellow fever throughout the West Indies and the littorals of the Caribbean Sea and the Gulf of Mexico; the cleaning of Rio de Janeiro and Santos resulted in the disappearance of the disease in Southern Brazil; and short campaigns in several of the principal cities of the Amazon River were followed by the apparently complete blotting out of yellow fever in the entire Amazon Valley! Upon these observed results there was built a simple epidemiology of yellow fever, and from this simple epidemiology the dream took shape that yellow fever might disappear forever from the American continent through the temporary organization of anti-aegypti measures in the largest cities of the few remaining endemic foci.

Shortly after the founding of The Rockefeller Foundation, the International Health Board became interested in the early realization of this dream, and General Gorgas was invited to undertake the task of determining which were the remaining key-centers of infection to be sanitated, and of collaborating with the respective governments in the organization of the necessary campaigns. Between 1915 and 1919, in spite of the interruption caused by the participation of the United States in the World War, preliminary surveys were carried out, and what was to have been the final drive for the elimination of the disease was begun. A noteworthy response was made by the governments of the continent, and adequate authority and funds were available to carry out the proposed measures.

During the first decade of Foundation collaboration in the control of yellow fever, 1915–1925, the disease receded on all fronts and, with only minor and apparently unimportant exceptions, obeyed implicitly all the rules which had been laid down for its behavior. These rules have fortunately been outlined for us by Dr. Henry Rose Carter in a work written shortly before his death in 1925.[2] This careful and devoted student of yellow fever, coworker with General Gorgas in many important campaigns, during a lifetime spent in yellow fever work, had an unequalled opportunity for close personal contact with the disease. Carter says:

*Author's preface*—We know quite well the conditions necessary for the existence of yellow fever, for it to become epidemic and to continue at any place; and when we find its existence or an epidemic reported where the conditions necessary therefor do not exist, we know that the disease reported as such is not yellow fever.

(page 3) *Yellow fever is contracted by man in nature from the bite of a mosquito, Aëdes (Stegomyia) aegypti (Linnaeus), itself infected by having fed on a man sick of that disease, and, so far as known, is in nature only thus contracted.*

(page 7) . . . and, owing to the invariable disappearance of yellow fever when this species (*Aëdes aegypti*)—and this species alone—is sufficiently controlled, it seems quite certain that in the Americas no other mosquito closely associated with man is a vector.

(page 50) . . . It is a disease of collections of men—civic rather than rural.

(page 71) . . . The duration of an epidemic, or even the infection of yellow fever at any place is limited *unless new human material*

*be supplied,* and this independently of climatic conditions.

But during the decade 1926 to 1936, which may well be termed the age of disillusion and partial enlightenment for yellow fever epidemiologists, yellow fever has refused to abide by these rules and has not continued to disappear from the continent in spite of the most conscientious application of methods previously so successful. The development of methods for the routine diagnosis of unsuspected fatal cases and for the identification by the protection test of those who have suffered infection has resulted in the revelation that yellow fever exists widespread throughout vast areas in the interior of South America under conditions previously considered incompatible with its existence.

Although the tenets of Gorgas and Carter are undoubtedly true for certain regions, it has been amply proved during the past few years that they do not hold for yellow fever in South America. Yellow fever does not invariably disappear when the *Aëdes aegytpi* mosquito is sufficiently controlled, and the duration of infection in many districts is not dependent upon the introduction of non-immune human elements into these districts. Yellow fever may occur under a great variety of conditions, and the factors determining its occurrence are in large part still undetermined. Yellow fever has been observed in the complete absence of the *Aëdes aegypti* mosquito as scattered cases in such sparsely populated rural and jungle areas that the continuance of the disease in these areas cannot be attributed to the occurrence of human infections.

This report presents a short résumé of the efforts to control yellow fever in South America since 1920 and of the observations which have resulted in important modifications of our knowledge of the epidemiology of this disease.

## RÉSUMÉ OF YELLOW FEVER CONTROL IN SOUTH AMERICA, 1920–1929

In 1919 it was believed by the closest students of the disease that the only important distributing foci of yellow fever infection in South America were the city of Guayaquil, Ecuador, on the Pacific Coast, and, on the Atlantic Coast, a small area of Northeast Brazil, extending as far south as the city of Salvador, Bahia. Antimosquito measures had been organized in Guayaquil in 1918,[3] and these measures resulted in the disappearance of the disease in 1919 from this city which since 1750 had been notorious as a center of infection. Campaigns in Northern Peru in 1920–1921 [4] were equally successful, and no known outbreaks of yellow fever have since occurred on the Pacific Coast of South America.

The known remaining focus of infection on the Atlantic seaboard had been attacked in 1919 through a federal sanitary commission organized by the Brazilian Government for work against yellow fever in all states lying within the known endemic focus. Unfortunately no adequate report has ever been published of the work done by the Commissão Sanitaria Federal during 1919 and 1920, and only those who came into personal contact with that effort can fully appreciate its scope and sincerity. But a partial report of the work in Pernambuco [5] made before the failure of this effort was apparent, contains the following significant paragraph, which is quoted in translation from the Portuguese:

> Yellow fever constitutes in the north of the country (Brazil) a problem much more difficult of solution than was believed; the dissemination of the virus extends over a large area, both within and outside the cities, in sparsely populated points, and, at times, failing to obey in a most disconcerting manner

the epidemiological rules which belong to yellow fever, to the point of suggesting a morbid entity not yet catalogued, were it not for the unusual dissemination of *Stegomyia calopus (Aëdes (Stegomyia) aegypti)* in those regions together with the clinical observations and autopsies made by persons well trained in the subject of yellow fever.

During 1922 it became very apparent that this federal campaign, which had been largely if not totally discontinued at the end of 1920, had failed of its objective and that yellow fever was still an important problem in Northeast Brazil. In 1923 The Rockefeller Foundation accepted an invitation to undertake the solution of the yellow fever problem in Brazil, and before the end of the same year Dr. Joseph White, veteran of many battles with yellow fever including and following the New Orleans campaign of 1905, had begun operations. Investigations were made and antimosquito measures were undertaken at all the principal coastal cities between Rio de Janeiro on the south and Manãos, the chief inland port of the Amazon Valley. No evidence was found of recent yellow fever south of Bahia or north of Ceará, and undivided attention was finally given to the region between these points.

Yellow fever dwindled on all sides, and by 1925 it was believed that the end of yellow fever on the American continent was in sight. It is true that an unexpected outbreak of the disease had been observed in Bucaramanga, Colombia, in 1923,[6] with no satisfactory answer to the question of the origin of the virus; but in the face of absolute quiet elsewhere on the continent during a period of 2 years, and the increasingly favorable picture encountered in North Brazil, the final solution of the yellow fever problem on the continent was anticipated in the immediate future.

The year 1925 has been mentioned as the end of the Golden Age of yellow fever epidemiology. That such was the case was not, however, fully apparent until some years later. The 1926 outbreak of yellow fever, which embraced the interior of several states of Northeast Brazil was attributed to the movement of non-immune troops through the region, lighting up and fanning to a visible flame the dying embers of infection which otherwise would have spontaneously disappeared. The intensification of antimosquito measures was followed by a rapid decline in the number of reported cases, and in 1927 Dr. M. E. Connor, who had taken over the technical direction of the service late in 1926, was able to report, after a survey trip covering the entire coast from Bahia to Pará, the Amazon Valley from the mouth of the river to Manãos, and the São Francisco Valley to Pirapora, that he could find no evidence of yellow fever activity. The renewed optimism, born of the failure to recognize cases of yellow fever anywhere on the continent during 11 months, was rudely shattered by single yellow fever positive autopsies in the States of Sergipe and Pernambuco in March and April, 1928, and by the discovery in May of the same year that the virus of yellow fever had again found its way into Rio de Janeiro, the federal capital, after an absence of 20 years.

The events of the months immediately following the discovery of yellow fever in Rio de Janeiro, one of the principal ports of South America, fully confirmed the great importance attributed to large centers of population, especially seaports, in the epidemiology of aegypti-transmitted yellow fever. Before the Rio de Janeiro outbreak terminated in July, 1929, locally infected cases had been recorded in the states of São Paulo, Minas Geraes, Rio de Janeiro, Bahia, Sergipe, Pernambuco, and Pará, and cases infected elsewhere had been seen at various ports between

Buenos Aires on the south and the inland port of Manãos, a thousand miles up the Amazon.

The rapidity of the decline of visible yellow fever following the suppression of the Rio de Janeiro outbreak was noteworthy, and between July, 1929, and March, 1930, less than a dozen cases were recorded for all Brazil. How optimistic was the reaction to this striking recession of yellow fever late in 1929 may be ascertained from the following paragraphs of the Annual Report of the Yellow Fever Service (unpublished) for the year 1929:

> (page 3) (b) The history of the march of yellow fever gathered from available data indicates the centers where the infection might be expected to remain for an indefinite period in the absence of sanitary intervention. Such centers proved to be the capitals and here intensive efforts are practised. Additional services are started for interior areas whenever there is need for same and continued until the situation is again normal or local officials take up the work.
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> (page 9) . . . For the first time in the history of yellow fever prophylaxis, control measures are being applied in all centers where this disease was present or was menacing.

### UNEXPECTED OUTBREAKS IN COLOMBIA AND VENEZUELA, 1929

While the situation in Brazil was occupying the attention of those responsible for its study and control, two totally unexpected and, at that time, unexplained outbreaks of aegypti-transmitted yellow fever were registered in Colombia and Venezuela, both in 1929. These outbreaks came at isolated points in the interior, completely out of contact with each other and with other known foci of infection. The place of one of these epidemics, Socorro, Colombia,[6] is a small town in the mountains east of the Magdalena River in the same general region as Bucaramanga, where the last previously recorded outbreak in Colombia had occurred 6 years before. The Venezuelan outbreak occurred in a series of small towns in the Cuyuni Valley, close to the towns of Guasapati and Tumeremo. This outbreak, like that at Socorro, cannot be linked in any way with the 1929 dissemination of virus from Rio de Janeiro.

### DEVELOPMENT OF NEW EPIDEMIOLOGICAL TOOLS

For a proper understanding of developments since 1929, it is necessary to digress long enough to compare the tools with which epidemiologists worked before 1930 with those available today. Previous to 1930, knowledge of the distribution of yellow fever depended upon the occurrence of outbreaks of sufficient severity to be declared by local authorities. Acceptable diagnosis depended upon the demonstration of a series of cases with the classical symptoms of yellow fever occurring under those conditions considered necessary for its existence. Final judgment was suspended on isolated suspect cases awaiting the occurrence of other cases in the neighborhood, and such was the faith in the epidemiological picture of the disease that the failure to find other cases or the failure to find aegypti were at times the basis for deciding against a diagnosis of yellow fever. Knowledge of the disease was largely based on observation of its manifestations among immigrants in endemic areas and among non-immune populations during its occasional excursions outside of endemic zones. Epidemiological surveys were limited to a study of mortality statistics and conversations with the medical profession and with local authorities, and such surveys were thought sufficient to indicate the presence or absence of the infection in an area. Even as late as 1928, the epidemiological picture of yellow fever

was held to be more concrete and definite than the pathology of the liver of the yellow fever patient.

The events of 1928 and 1929, however, had shown that the pathological diagnosis based on the microscopical examination of liver tissue merits great respect, and the wealth of material obtained during the Rio de Janeiro outbreak established on a firmer basis among epidemiologists the belief that the pathological picture in the yellow fever liver is not duplicated by that of any other acute infectious disease. In 1930 [7] the examination of liver tissue, which had previously been used in suspect cases, was introduced as a routine measure for discovering unsuspected fatal cases of yellow fever in otherwise silent endemic areas.

Although the virus of yellow fever had been successfully established in laboratory animals in 1927 [8] it was not until 1931 that the perfection of the mouse protection test [9] enabled the epidemiologist to study the distribution of immunity to yellow fever on a large scale to delimit existing endemic areas, and not until 1935 was the easily transported mouse shown to be readily infectible with the virus of yellow fever from human cases in the field.

## YELLOW FEVER CONTROL IN NORTHEAST BRAZIL, 1930–1936

When the speaker became responsible in June, 1930, for the technical administration of the Coöperative Yellow Fever Service jointly maintained by the Brazilian Government and The Rockefeller Foundation, it was already apparent that the brief optimism of a few months before was not justified. Yellow fever had just been shown to be present in the State of Rio de Janeiro in the south, in the State of Pernambuco in the northeast, and in the State of Pará at the mouth of the Amazon River. The most important control problem to be attacked was whether further extension of antimosquito measures to smaller towns would result in the elimination of yellow fever, which "key-center" control had failed to accomplish, and the most important epidemiological problem seemed to be to discover how the virus of yellow fever is maintained during periods of "invisibility."

The State of Pernambuco, a long, narrow area extending directly westward from the Atlantic Ocean, possesses in more or less well defined belts the various climatic conditions characteristic of Northeast Brazil, and was chosen for the initiation of intensified control measures and for special studies. An analysis of the available information regarding the distribution of yellow fever in Pernambuco previous to 1930 seemed to justify the division of the state into 4 rough epidemiological zones:

1. *Key-center Endemic*—Recife, the capital city and principal port, with a population of more than 250,000, a typical key-center of yellow fever infection which might be expected in the absence of antimosquito measures to maintain endemicity in and of itself, with the more or less constant occurrence of "visible" yellow fever in immigrants from non-endemic areas.

2. *Regional Endemic*—The heavily populated coastal plain, where important outbreaks of yellow fever were rarely reported but where the presence of the virus was from time to time made manifest through the infection of occasional foreigners.

3. *Endemo-epidemic* — A relatively heavily populated zone just back of the coastal plain, where yellow fever was frequently reported as sharp epidemics in the native population.

4. *Non-infectible*—The sparsely populated Sertão or hinterland comprising roughly the western half of the state, subject to occasional droughts of great

severity, with no history of yellow fever in the past.

The plan of campaign drawn up in June, 1930, called for the routine organization of anti-aegypti measures in all cities and towns of 2,000 population and over throughout the key-center endemic, the regional endemic, and the endemo-epidemic zones, leaving only the " non-infectible " zone without control. The extent to which this program differed from the original key-center theory of control can be appreciated when it is remembered that Carter [2, p. 20] states in discussing the spontaneous disappearance of yellow fever:

> It has disappeared from Cartagena, Barranquilla, Maracaibo, Cucuta (towns of from 20,000 to 75,000 people); from all of Hayti and Santo Domingo; from Porto Rico, St. Thomas and a host of smaller places; and this without any sanitary work and with aegypti abundant.

Only a few months intervened between the inauguration of this intensive program and the perfection of the viscerotome, an instrument for the rapid removal of pathological specimens post-mortem without autopsy [10] which made possible the extension of the routine collection of liver tissue from the bodies of persons dying in 10 days or less after onset of illness, for the diagnosis of unsuspected yellow fever. Viscerotomy confirmed the absence of yellow fever from Recife, the capital city, but revealed fatal cases in the *regional endemic,* the *endemo-epidemic* and " *non-infectible* " zones! In other words, key-center control in Pernambuco after 7 years' constant application had resulted in the elimination of yellow fever only from the key-centers worked!

The installation of anti-aegypti services in the towns of the eastern part of Pernambuco was followed by the rapid disappearance of positive diagnoses on liver tissue collected in this area. The theory of key-center control only needed application to smaller towns than had been previously worked to give the desired results. Not so in the Sertão! The organization of anti-aegypti measures was carried to smaller and smaller centers of population, until villages of less than 50 houses were being worked; but nevertheless, viscerotomy continued to reveal fatal cases in this " *non-infectible* " hinterland. After conclusive proof had been obtained that the disease would not spontaneously disappear from the rural districts, the so-called " fine-tooth-comb " method involving anti-aegypti measures in every home throughout rural districts was authorized for the Sertão. This method eventually gave satisfactory results, and since August, 1934, viscerotomy has failed to reveal yellow fever in Pernambuco or in the 5 neighboring states lying between the São Francisco and Parnahyba Rivers.

It should be noted here that, although Northeast Brazil has been more intensively studied than any other part of South America in recent years, no evidence of the occurrence of yellow fever without *Aëdes aegypti* has been found in that region, and, conversely, the disease has not continued long in those places where the incidence of this mosquito has been reduced by control measures.

The reason underlying the success of anti-aegypti measures limited to the cities and towns in the coastal plain and the failure of the same measures limited to towns in the interior merits discussion. Investigation has shown that the *Aëdes aegypti* mosquito, although widely disseminated throughout the towns and villages of the coastal plain, is not common in the rural habitations of this zone; on the other hand, the dry interior is unique among all the districts investigated in Brazil in that there is a high index of infestation with this mosquito in the rural homes

throughout a wide area. This exceptional distribution of *Aëdes aegypti* is attributed to the fact that the dryness of the climate obliges the inhabitants to store whatever water is to be had for domestic use. The containers used for storing water provide ideal breeding places for *Aëdes aegypti* once it has been introduced, and the custom, bred of necessity, among those travelling on business and on religious pilgrimages, of carrying drinking water containers, has provided the means of such almost universal introduction.

The experience in Northeast Brazil has confirmed the opinion expressed in the report of the Commissão Sanitaria Federal (*vide supra*) that yellow fever will not obey the epidemiological rules in the face of an unusual dissemination of *Aëdes aegypti* but has shown that the extension of anti-aegypti measures to strictly rural regions is practicable and efficacious. No evidence of the presence of yellow fever has been found in Northeast Brazil for more than 2 years, and control measures could probably be safely abandoned were it not for the danger of reinfection from nearby areas demonstrated to harbor the virus of yellow fever in the absence of aegypti and under conditions for which adequate methods of control have not yet been evolved.

### YELLOW FEVER WITHOUT AËDES AEGYPTI
### JUNGLE YELLOW FEVER

Although the demonstration in 1928 [11] that the virus of yellow fever can be transmitted in the laboratory by various species of mosquitoes found in Africa, other than *Aedes aegypti,* had been followed, as early as 1929,[12] by a similar demonstration for some of the South American species, it was not until 1932 [13] that the natural occurrence of yellow fever in the absence of aegypti was fully confirmed. The full significance of this first observation of yellow fever without *Aëdes aegypti* in the Valle do Chanaan, Espirito Santo, Brazil, was not understood at the time, since the spontaneous termination of the disease within a few weeks after coming under observation, when a very high percentage of the population of the valley was still non-immune, suggested that this outbreak had probably been due to a temporary excursion of the virus under relatively unfavorable conditions from nearby towns and cities where no yellow fever could be found but where high densities of aegypti and high percentages of immunes were encountered. Later observations of yellow fever without aegypti, to which the name jungle yellow fever has been given,[14] have suggested that it may be the more natural and permanent form of yellow fever and that the aegypti-transmitted type may be a highly exotic type maintained with great difficulty because of the tendency to burn itself out through the exhaustion of non-immune populations.

Scarcely had the outbreak in the Valle do Chanaan been identified when epidemiologists were astounded by an outbreak of yellow fever at Santa Cruz de la Sierra, Bolivia, a town of less than 20,000 population, completely isolated from other larger centers of population, lying in the heart of the continent more than 1,000 kilometers from any focus of infection known during the previous two decades. The Santa Cruz epidemic occurred in the presence of a high density of aegypti and responded rapidly to anti-aegypti measures, but no reasonable explanation of the source of virus for this outbreak was found until viscerotomy revealed some months later that yellow fever was present at San Ramón, a small Indian village of the lowlands of Bolivia, in a region in which *Aëdes aegypti* has not been found!

By 1933, immunity survey results

were available from various parts of the Amazon Valley indicating that yellow fever had not been absent from any large portion of the valley in the previous 20 years during which it had not been recognized. Likewise, independent protection test studies in Colombia [15] had suggested the maintenance of the virus of yellow fever in certain rural regions of the Magdalena Valley. Before the end of the year, viscerotomy had confirmed fatal cases of jungle yellow fever for the Magdalena Valley at Caparrapí and for the Amazon Valley at Lauro Sodré, close to the Brazilian, Colombian, and Peruvian frontiers.

The observations of jungle yellow fever previous to 1934, however, are relatively insignificant in comparison with those made during the years 1934, 1935, and 1936, which have shown that it is a very important epidemiological entity, not only as a factor in the preservation of the yellow fever virus, but also as a cause of illness and death among rural and jungle populations. Even those most intimately in contact with the work on yellow fever were totally unprepared for the rapidly unfolding epidemiological picture of the last 3 years. The events of these years include:

1. The discovery in 1934 of jungle yellow fever, confirmed by clinical observation, autopsy, immunity tests and isolation of the virus with reproduction of the disease in susceptible animals, at Coronel Ponce on the Planalto of Matto Grosso [16] 100 miles east of Cuyabá, the state capital. Yellow fever as an urban disease had been known late in the past century in Cuyabá, but there was no history of its occurrence anywhere in the state during the previous 30 years. An attempt to inculpate Cuyabá, and other towns of the state where high densities of *Aëdes aegypti* exist, as the source of virus for this rural outbreak failed in the face of negative histories substantiated by negative protection test results in the younger age groups of the population of these towns. However, immunity studies made on Indians at Simões Lopes, an isolated government post about 100 miles north of Coronel Ponce, showed high percentages of immunes among all age groups and suggested that the infection of the Planalto came from the jungle areas of the Amazon Valley.

The slow moving outbreak on the Planalto was carefully studied during 1934 and 1935. The scattered population of this region had apparently not been exposed to yellow fever in recent years, since histories of recent illness were obtained from all persons with positive protection tests. Investigation showed that the local popular idea that the new disease was contracted in the fields next to the uncut forest was well founded. The paucity of human population in this area and the time and space distribution of cases make it highly improbable that man was at any time an important source of virus for human infection or was an appreciable factor in the dissemination of the disease from one point to another. Positive protection tests obtained with the sera of wild monkeys [17] indicate that infection in this area has not been limited to human beings.

2. The final proof, by clinical observation, autopsy, and isolation of the virus in susceptible animals, that jungle yellow fever continues endemic in the Muzo region of Colombia, as had been suggested by previous protection test results.[15] Yellow fever was reported in Muzo even during the past century, but its careful differentiation from malaria and relapsing fever, both endemic here, was first made in 1907.[18] Since this early confirmation, cases of yellow fever among the non-immune

laborers brought from the highlands of Colombia to work the famous emerald mines of Muzo have been sufficiently numerous to cause repeated investigations but have not been numerous enough to explain the continued endemicity of the past 30 years in this sparsely populated region. Although *Aedes aegypti* was reported as present in Muzo in 1907, repeated investigations since have failed to confirm its existence anywhere in the area, and a careful reading of the early description leads to the conclusion that the classification was in error.[14] Epidemiologists who investigated Muzo during the quarter of a century following the first description of yellow fever there and before the introduction of the protection test, failed to convince themselves, in the absence of aegypti and of explosive outbreaks involving many cases, that the disease under investigation might be yellow fever! Even Gorgas,[19] following a visit to the mines in 1916, declared that the suspect cases which had caused his visit could not have been yellow fever, since the conditions necessary for endemicity did not exist.

Viscerotomy has resulted in the confirmation of cases at Muzo in March, June, and October, 1934; in December, 1935; and in January, April, and May, 1936. Cases have been limited, so far as is known, to persons who had intimate contact with the forest, only a few cases occurring at a time. The organization of viscerotomy throughout the surrounding region has shown that endemicity is not strictly limited to the immediate vicinity of Muzo but apparently covers a large sparsely populated district on the right bank of the Magdalena River, between this river and the high mountain ranges to the east. The proof that this district harbors endemic jungle yellow fever offers at last an acceptable source of virus for the unexplained outbreaks, occurring after periods of several years of apparent absence of the disease from Colombia, in Bucaramanga in 1923, and in Socorro in 1929, both of which towns are within a short distance of the known endemic district.

Muzo is unique in that it has a definite history of constant endemicity of jungle yellow fever during at least 30 years; it is probable that the recently isolated Muzo strain of virus has not been transmitted by the *Aëdes aegypti* mosquito during this period.

3. The identification of a rural epidemic in 1934 on the eastern slope of the Andes at Restrepo, just at the edge of the llanos in Colombia, as yellow fever. This general region, which lies in the drainage basin of the Orinoco River, had in 1886 suffered[6] an outbreak suspected of being yellow fever, but there was no historical reason for believing this to be an endemic region. Careful investigation has shown that even the larger towns of the region are not even now infested with aegypti, and although cases have continued to be recorded during the years 1935 and 1936, some of which have apparently been infected almost at the edge of the towns, no cases are known to have been infected in the towns themselves.

4. The diagnosis, through viscerotomy, of 4 isolated cases—1 in May, 1 in June, and 1 in July, 1934, and 1 in May, 1935—within a comparatively small area on the Ilha Marajo, the large island lying at the mouth of the Amazon River.[20] Careful investigation has indicated that some undiagnosed cases may have occurred, but has failed to bring any clinical cases under observation. The circumstances strongly suggest that there is some reservoir of virus in this region quite independent of the human population.

5. The demonstration that the anti-aegypti campaign, begun in the lowlands

of Bolivia in 1932 at Santa Cruz de la Sierra, had probably not had any important effect in limiting the distribution of the jungle virus, although only 1 case was diagnosed by viscerotomy in Bolivia in 1933, and none were found during 1934. Yellow fever without aegypti was shown to be present in the war zone south of Santa Cruz in 1935. The present year, 1936, has been a banner year for viscerotomy in Bolivia, and diagnosis of yellow fever based on liver examination has been made at numerous points on all sides of Santa Cruz, at many places in the foothills of the Andes, at San Ramón and San Javier in the San Miguel River Valley, at Trinidad on the River Mamoré, at Huichini, on the River Beni, and at Cobija, on the frontier of the Territory of Acre, Brazil.

6. The observation during 1935 and 1936 of an extensive outbreak of jungle yellow fever involving the southern part of Goyaz, the western and southwestern parts of Minas Geraes, a large part of the state of São Paulo, the northern part of Paraná, and the southern part of Matto Grosso. Most of the territory covered by this outbreak had never previously reported yellow fever, and none of it was known to have produced cases during more than a quarter of a century. The area is far from uniform in topography and density of population, and ranges from sparsely settled regions where there are a few settlers along the river valleys, to very rich densely populated districts. The known infected district covers several hundred thousand square miles; it is impossible even to hazard a guess as to the number of cases which have occurred, beyond stating that it is known to be in the thousands. This is by far the most important and extensive outbreak of jungle yellow fever yet observed and is responsible for a new conception of the threat this disease represents for rural populations throughout much of South America.

7. The occurrence of small isolated outbreaks of aegypti-transmitted yellow fever under circumstances strongly suggesting that the virus for the production of such outbreaks had come from nearby areas of jungle infection. Outstanding examples of such outbreaks are that of Theofilo Ottoni in the state of Matto Grosso, Brazil, in 1935,[20] and that of Cambará, in the state of Paraná, in 1936.

## DISCUSSION OF JUNGLE YELLOW FEVER

There is ample reason for believing that aegypti-transmitted yellow fever and jungle yellow fever are identical except for the conditions under which infection occurs. The identity of the disease occurring in the absence of aegypti in the Valle do Chanaan, in Matto Grosso, in Goyaz and in both the Magdalena and Orinoco River Valleys in Colombia, has been fully established by clinical observation, autopsy, protection test, and isolation of the causative virus with reproduction of the disease in susceptible animals. Furthermore, the jungle virus has been transmitted from monkey to monkey in the laboratory by the *Aëdes aegypti* mosquito[21] just as the urban virus has been transmitted by various jungle mosquitoes. Aegypti-transmitted yellow fever is largely a house disease, since the vector breeds and spends its entire life either in or in immediate proximity to human habitation; the close contact between vector and cases in the home results in building up a high concentration of virus in the vector; thus most of the non-immune members of the household become infected before the disease dies out because of a shortage of new cases to infect succeeding generations of the short lived vector.

In jungle yellow fever, on the other hand, man is not an important source

of virus for the infection of human cases; the human case is apparently an accident in the course of some as yet unknown extra-domiciliary cycle of infection. In support of this idea, studies of immunity distribution in wild animals in South America have already shown that animals of various types,[14, 17, 22] including opossums and several species of monkeys, may acquire immunity under natural conditions in the jungle.

Much further study is necessary before the entire story can be known; the demonstration of one cycle of infection in the jungle should not be interpreted to exclude other cycles, and a thorough search must be made for all possible blood-sucking vectors and all possible vertebrate hosts. The possibility of virus reservoirs consisting of long lived vectors, vectors capable of transmitting the virus from generation to generation, or even vertebrates incapable of acquiring immunity and therefore permanent reservoirs of the virus, when once infected, must be investigated.

The questions most frequently asked by those who learn for the first time of the recent developments in the epidemiology of yellow fever are, "Is jungle yellow fever a recent adaptation of the virus of yellow fever to non-domestic conditions?" and "If not a recent development, how could jungle yellow fever escape observation and description in the past?"

The answer to these two questions is that jungle yellow fever is not a recent adaptation but may even be the original and natural form of yellow fever and that it did not entirely escape observation and description in the past. There are two quite convincing descriptions of yellow fever from former times and a third, published many years after the observations on which it is based, which undoubtedly refer to what is now known as jungle yellow fever.

The first description of this kind which has come to my attention is the report[23] of an investigation made in 1887 among the Catholic missions along the foothills of the Andes south of Santa Cruz de la Sierra, Bolivia. A series of cases diagnosed as yellow fever by a clinician familiar with the disease in Cuba, is described at Abapó, El Espiño, Muchirí, and Masaví, in exactly the same region in which yellow fever without aegypti was encountered among the troops in the trenches in 1935. Quite naturally this early report carries no reference to the presence or absence of *Aëdes aegypti*, since it was written some 13 years before the transmission of yellow fever by this mosquito was first demonstrated. The authors realized that their diagnosis would be criticised and probably not accepted, as indeed it was not, no reference to this report reaching the international literature until after the discovery of yellow fever in Santa Cruz in 1932. To quote in translation from the Spanish:

> Without doubt many authorities will be unwilling to admit the presence of yellow fever, isolated in the heart of Bolivia, far from the places in which yellow fever generally exists and without known routes of penetration from without.

These words fittingly describe the difficulties of accepting the same diagnosis in this same area 45 years later. That this last outbreak should not have been unexpected is suggested by the fact that the 1887 epidemic was apparently not the first. To quote in translation:

> The older inhabitants state that Abapó was stricken some 20 years ago by a disease which presented these same symptoms and which Dr. José Lorenzo Sanchez, who was then in charge of the local parish, called yellow fever. Likewise this year, it was a priest who announced the true name of the disease. The virtuous Señor Sarrazona, the priest at Abapó, who was to be one of the first to

pay tribute to the scourge, styled it, as a good Spaniard would, Black Vomit.

The second description of jungle yellow fever is that made at Muzo, Colombia, in 1907.[18] The careful clinical observations then recorded do not permit any doubt that yellow fever was present and the epidemiological notes point conclusively to jungle yellow fever. To quote in translation:

(a) It is contracted in the forest and not in the neighborhood of the houses.

(b) It is transmitted by *Stegomyia calopus* and probably also by other culicines.

(c) Inoculation takes place during the daylight hours, which are spent by the workers in places where the transmitting mosquitoes predominate.

Except for the statement that "*Stegomyia calopus*" (*Aëdes aegypti*) was present, the description of yellow fever as given for Muzo in 1907 can stand as a true description of the jungle yellow fever observed there in 1934, 1935, and 1936. That the mosquitoes diagnosed as *Stegomyia calopus* were not *Aëdes aegypti* is clearly indicated by the description of the habits of these mosquitoes and the failure of numerous investigations between 1916 and 1936 (*vide supra*) to reveal this mosquito at Muzo.

In addition to these descriptions there is the reference made in 1929 [24] to two outbreaks many years before in the State of São Paulo, Brazil, reputed to have occurred in the absence of aegypti. This reference, made several years before the observations in the Valle do Chanaan, is very interesting in that it describes so closely the conditions under which jungle yellow fever has recently been found.

The first of these outbreaks, of which I know only from the reports of others, occurred in an Indian village on the Rio Verde. In the other case which I personally investigated, yellow fever was found in some huts built in the midst of the forest and inhabited by laborers. These men were cutting the forest in preparation for the construction of a railroad which was to join Funil to Campinas. I examined several huts from which had come cases of yellow fever, without finding any trace of larvae or adults of *Stegomyia*, although forest mosquitoes were present. This observation is especially interesting since it has lately been shown in Africa that transmission may occur through mosquitoes other than the domesticated stegomyia. This latter will always be among us the most important vector and the transmission by other species must be rare and exceptional, but nevertheless the determination of other species which may transmit the virus is an interesting problem.

During the last few years, *Aëdes aegypti* has not been the most important vector but may be expected rapidly to regain its dominant position should anti-aegypti measures be abandoned. Paradoxically, one of the most important results of the observation of endemicity without aegypti has been to emphasize the need of permanent anti-aegypti services throughout endemic areas and in regions in close contact with endemic areas. And today it is true that the entire continent is, through the development of rapid transportation facilities, in close contact with endemic areas. With present facilities it would be possible for the members of this Association to leave New Orleans, visit a known infected region, probably seeing active cases, and return to the United States, all within the generally accepted 6 day incubation period of yellow fever. The situation is not one calling for undue alarm, but it is one which merits careful evaluation of the implied threat of possible extension of infection.

SUMMARY

Work during recent years in South America has shown that—

1. Elimination of yellow fever from the larger "key-centers" of population by anti-mosquito measures will not result in the disappearance of the disease from the continent.

2. Aegypti-transmitted yellow fever may, under the conditions prevailing in Northeast Brazil, maintain itself for long periods of time as a rural disease requiring organization of anti-aegypti measures in strictly rural districts for its elimination.

3. There exists throughout vast areas of the continent, a previously unsuspected epidemiological type of yellow fever to which the name "jungle yellow fever" has been given. Jungle yellow fever differs from the classical disease in that it occurs in the absence of *Aëdes aegypti,* and under conditions previously considered incompatible with yellow fever endemicity.

4. Jungle yellow fever, in the absence of adequate methods for its control, must be considered as a possible permanent source of virus for the re-infection of cities and towns where high densities of *Aëdes aegypti* are tolerated.

REFERENCES

1. Reed, Walter; Carroll, James; and Agramonte, Aristides. Experimental Yellow Fever. *Trans. Assn. Am. Phys.,* 16:45-70, 71, 1901.

2. Carter, Henry Rose. *Yellow Fever: An Epidemiological and Historical Study of Its Place of Origin.* Williams & Wilkins, 1931.

3. Connor, M. E. Yellow Fever Control in Ecuador. *J.A.M.A.,* 74:650 (Mar. 6), 1920.

4. Carter, Henry Rose. Yellow Fever in Peru: Epidemic of 1919 and 1920. *Am. J. Trop. Med.,* 2, 87-106 (Mar.), 1922.

5. Correa da Costa, Clovis. Febre Amarella. Notas sobre os trabalhos da Commissão Sanitaria Federal em Pernambuco. *Arch. Brazileiros de Medicina,* 1920.

6. Pena Chavarria, Antonio; Serpa, Roberto; and Bevier, George. Yellow Fever in Colombia with Special Reference to the Epidemic in Socorro in 1929. *J. Prev. Med.,* 4:417-457 (Nov.), 1930.

7. Soper, F. L.; Rickard, E. R.; and Crawford, P. J. The Routine Post-mortem Removal of Liver-Tissue from Rapidly Fatal Fever Cases for the Discovery of Silent Yellow Fever Foci. *Am. J. Hyg.,* 19:549-566 (May), 1934.

8. Stokes, A.; Bauer, J. H.; and Hudson, N. P. Experimental Transmission of Yellow Fever to Laboratory Animals. *Am. J. Trop. Med.,* 8:103-164 (Mar.), 1928.

9. Sawyer, W. A.; and Lloyd, W. The Use of Mice in Tests of Immunity Against Yellow Fever. *J. Exper. Med.,* 54:533-555 (Oct.), 1931.

10. Rickard, E. R. The Viscerotome, an Instrument for the Removal of Fragments of Liver for Pathological Examination without Autopsy. *Rockefeller Foundation Quart. Bull.,* 5:310-320 (July), 1931.

11. Bauer, J. H. The Transmission of Yellow Fever by Mosquitoes other than *Aëdes aegypti. Am. J. Trop. Med.,* 8:261-282 (July), 1928.

12. Davis, N. C.; and Shannon, R. C. Studies on Yellow Fever in South America: V. Transmission Experiments with Certain Species of *Culex* and *Aëdes. J. Exper. Med.,* 50, 803-808 (Dec.), 1929.

13. Soper, F. L.; Penna, H.; Cardoso, E.; Serafim, J., Jr.; Frobisher, M., Jr.; and Pinheiro, J. Yellow Fever without *Aëdes aegypti.* Study of a Rural Epidemic in the Valle do Chanaan, Espirito Santo, Brazil, 1932. *Am. J. Hyg.,* 18, 555-587 (Nov.), 1933.

14. Soper, F. L. Rural and Jungle Yellow Fever. A New Public Health Problem in Colombia. *Rev. de Higiene, Bogotá,* 4:47-84 (May-June), 1935.

15. Kerr, J. A.; and Patino Camargo, L. Investigaciones sobre fiebre amarilla en Muzo y en la región de Santander. *Rev. de Higiene, Bogotá,* 2:63-91 (Mar.), 1933.

16. Burke, A. W. An Epidemic of Jungle Yellow Fever on the Planalto of Matto Grosso, Brazil. In preparation.

17. Soper, F. L. Jungle Yellow Fever: A New Epidemiological Entity in South America. *Rev. de Higiene e Sande Publica,* Rio de Janeiro, 10:107-144 (Apr.), 1936.

18. Franco, R.; Martiez Santamaria, J.; and Toro Villa, G. Fiebre Amarilla y Fiebre Espiroquetal. Academia Nacional de Medicina, *Sesiónes* scientificas del Centenario, Bogotá, 1911.

19. Gorgas, W. C. *Rev. de Higiene, Bogotá,* 8 (Jan.), 1917.

20. Soper, F. L. Recent Extensions of Knowledge of Yellow Fever. *Quart. Bull. Health Organization of the League of Nations,* 5:19-68 (Mar.), 1936.

21. Whitman, L. 1935. Personal communication.

22. Wilson, D. B. 1936. Personal communication.

23. Ortiz, Nicholás, and Camó Montobbio, Jose. Fiebre amarilla en Bolivia, 1887. Original report reprinted in *La Revista del Instituto Medico,* Sucre, Bolivia, 1932.

24. Lutz, Adolpho. Reminiscencias da febre amarella no Estado de São Paulo. *Memorias do Instituto Oswaldo Cruz,* 24, No. 3, 1930.