CHAPTER 1

Monkeys and Yellow Fever

PEDRO GALINDO

I. The Rhesus Monkey and Early History of Yellow Fever Research 1
   II. The Role of the New World Monkeys in Yellow Fever Research 3
       A. Historical 3
       B. Experimental Work with Monkeys and Yellow Fever 7
       C. Field Observations on Monkeys and Yellow Fever 10
       D. Monkeys in the Detection of Jungle Yellow Fever 12
   III. Monkeys and Yellow Fever in the Future 14
       References 15

I. The Rhesus Monkey and Early History of
   Yellow Fever Research

Yellow fever occurs in Africa and the Western Hemisphere tropics. It
has also caused great epidemics in the temperate zone of the New World.
It was one of the world's great plagues for several centuries.

It is now known that there are two different types of this disease. The
virus causing the disease is the same but the hosts and insect vectors
usually are different. Urban yellow fever occurs in city dwellers and is
transmitted by the domesticated mosquito, Aedes aegypti. Jungle yellow
fever has monkeys as its usual important hosts and is transmitted by
jungle-breeding, usually arboreal, mosquitoes. It has been only recently,
after the great epidemics in the cities abated, that the emerging picture of
jungle yellow fever began to take shape. However, monkeys played an
important part in the early development of knowledge about yellow fever,
even in the urban type, and are more importantly involved now in the more common jungle type.

Reed (1902) in Cuba produced yellow fever in a human volunteer by injecting filtered serum from another infected human. Thus for the first time, a filtrable virus was proven to be the cause of a specific human disease.

Reed and his commission in Cuba also proved that the virus was transmitted by a mosquito then called Stegomyia fasciata (now known as the Aedes aegypti) and that the disease could be transmitted by the mosquito only under certain conditions. These findings indicated the necessity for the control or eradication of the insect vector, which led to the eradication of yellow fever from Cuba and many other populated areas of the Western Hemisphere. Associated with the control of the malaria-bearing mosquitoes, belonging to a different genus, these measures eradicated yellow fever and almost eradicated malaria from the Canal Zone in Panama making the construction of the Canal possible.

After it was known that yellow fever virus grows in man and is transmitted by mosquitoes, it then became important to find experimental animal hosts to study the disease in more detail. Great efforts were displayed by scientists of the Rockefeller Foundation in Africa during the third decade of this century to unravel some of the mysteries involved in the epidemiology of this disease. In 1927 members of the West African Yellow Fever Commission, produced the disease in an Indian monkey, Macaca mulatta by injecting it with the blood of an ailing West African named Asibi. This first transmission of the yellow fever virus to a non-human animal opened up entire new possibilities for research (Stokes et al., 1928). The strain of yellow fever virus isolated from this rhesus monkey became known as the Asibi strain, after its human donor, and has been one of the most widely used strains in yellow fever research. It was also the strain which eventually gave rise to development of the vaccine. In the same year it was shown that yellow fever could be transmitted from monkey to monkey by Aedes aegypti.

Laboratory-acquired infections of yellow fever sometimes resulted fatally. The world lost some of its most brilliant scientists in its battle against yellow fever. The names of Lazear, Stokes, Noguchi, Young, Lewis, Cross, and Hayne, among others, stand out in the history of medicine as true heroic soldiers, who, above and beyond the call of duty, gave their lives trying to conquer one of the worst scourges of mankind. Some form of immunization was urgently needed. Dr. Sawyer and his associates of the International Health Division, Rockefeller Foundation, observed that monkeys inoculated with highly virulent strains of yellow fever virus 4–6 hr following an injection of yellow fever immune serum possessed a solid
permanent immunity after the passive immunity had disappeared. By this time Theiler had successfully adapted the Asibi virus to mice and had produced a new strain with all the properties of the yellow fever virus but completely harmless to monkeys. This mouse-adapted strain became known as 17D. Dr. Sawyer, using the 17D strain, devised a vaccine consisting of a 10% suspension of infected mouse-brain tissue in fresh human immune sera. This material, when used with supplementary immune sera, gave solid immunity in monkeys without the development of symptoms. After thorough testing in monkeys, 10 persons were vaccinated in May and June 1931. This was the first vaccine against yellow fever. After its improvement and introduction into public health services, no further cases of the disease occurred among workers involved in yellow fever research. The mass vaccination of people throughout the tropics helped in averting development of the devastating urban epidemics which swept the western world from the sixteenth through the nineteenth century.

After the brilliant discoveries in yellow fever by Finlay, Reed, Lazear, Carroll and Agramonte in Cuba and the successful control work against the disease by Gorgas and Chagas in Cuba, Panama, and Brazil, the lime-light of yellow fever research had passed from America to Africa. During the fourth decade of this century the stage for some of the most dramatic episodes in the history of yellow fever shifted back from the Dark Continent to the New World.

This does not mean that yellow fever research in Africa came to a stand-still. During the last 30 years, through the continued efforts of the West African Yellow Fever Commission of the Rockefeller Foundation and of the East African Virus Research Institute at Entebbe, Uganda, many important advances in our knowledge of the epidemiology of yellow fever have been made. This work has contributed, in particular, to a clear understanding of the basic ecologic differences that exist between the African and the American manifestations of the disease.

II. The Role of the New World Monkeys in Yellow Fever Research

A. HISTORICAL

Yellow fever was a well-known pathologic entity in the Western Hemisphere during the seventeenth century (Carter, 1931), but it was not until early in the twentieth century when its viral etiology and the mosquito-borne nature of the disease became firmly established (Reed, 1902). The discoveries of the U. S. Army Yellow Fever Commission in Cuba led to
development of the "Gorgas doctrine," which postulated that yellow fever could not exist in the absence of the highly domestic mosquito, *Aedes aegypti*, then known as *Stegomyia fasciata*, and that adequate control of this insect would invariably lead to eradication of the disease.

Franco et al. (1911) advanced the first hints that human cases of yellow fever could be contracted in uninhabited jungle areas, when they reported on an epidemic outbreak which occurred in Muzo, Colombia in 1907. They concluded that the cases they studied had contracted the disease during daylight hours while working in the forest and that the vector had been *Stegomyia calopus* (= *Aedes aegypti*). This last statement invalidated their finding for many years, because the mosquito they reported as a forest vector was known to be strictly a house mosquito in the Western Hemisphere. More recent investigations indicate that Dr. Franco and associates probably mistook a forest mosquito common in the area, *Aedes dominici*, for *A. aegypti*.

One of the first positive reports of the existence of a jungle form of yellow fever, with possible involvement of monkeys as natural hosts of the virus, was that of Balfour (1914). Instructed by Dr. Patrick Manson to look for possible reservoirs of yellow fever among the lower animals of the Western Hemisphere, this scientist picked up stories in Trinidad that old residents could always tell when there was going to be an epidemic of yellow fever because, prior to its appearance, red howler monkeys were found dead and dying in the "high woods." Dr. Balfour confirmed these stories from reliable sources and was able to trace back some human cases to infection in the jungle. Balfour's observations in Trinidad were confirmed many years later by Downs (1955).

The epidemiologic term "jungle yellow fever" was coined by Soper et al. (1933) in reporting an outbreak of yellow fever in the Valle do Chanaan, Brazil, among woodcutters and agricultural workers who acquired the disease while working in or near the forest during the daytime and in the complete absence of the mosquito *Aedes aegypti*. Monkeys were not specifically mentioned in this report as possible sources of virus. However, the existence of natural vertebrate hosts other than man was implied by the authors who stated: "... man may not be an essential factor in the continuance of endemicity nor in the spread of the virus."

The discovery of jungle yellow fever in Valle do Chanaan, was followed by numerous studies of similar outbreaks in other areas of Brazil and of Colombia. In 1934, monkeys were found for the first time to be natural hosts of the virus, when five white-faced monkeys, captured in the jungles of Brazil, were found to have naturally acquired immunity against the yellow fever virus (Levi Castillo, 1948). The first isolations of the virus from the blood of naturally infected monkeys were reported by Laemmert
and Castro-Ferreira (1945), who isolated it from several marmosets captured in the jungle in the vicinity of Ilheus, Brazil.

Up until 1948 outbreaks of jungle yellow fever had occurred in South America. In November and December 1948, “like a bolt from the blue,” yellow fever reappeared in Panama in the jungle form, killing five farmers who contracted the disease along the edge of the Pacora woods, scarcely 15 miles east of Panama City (Elton, 1952). The last autochthonous case of yellow fever, prior to 1948, was diagnosed in Panama during the year 1905.

The yellow fever virus moved further east in 1949 reaching the shores of the Panama Canal and killing additional persons there. Early in 1950 the virus managed to cross the Canal, appearing on the western shores of this natural and artificial barrier, which normally blocks passage of yellow fever from South to Central America. From here a typical wave of jungle yellow fever was to start on a long, slow, but relentless journey north that was to reach the border area between Guatemala and Mexico in 1956. This wave left in its wake hundreds of human deaths and utter destruction of the howler monkey population, whose cadavers left the woods reeking with the odor of dead animal flesh (Trapido and Galindo, 1956).

Despite the sequelae of death and devastation that this wave of jungle yellow fever left behind, many important points on the ecology of the disease were elucidated during its passage through Central America.

In June 1951 clinical diagnosis of a human case was made by the late Dr. Gustav Engler at the Almirante Hospital. A serum sample from this patient was sent to Dr. Enid de Rodaniche of Gorgas Memorial Laboratory, who isolated from it a strain of yellow fever virus. This became the first time that this virus had been isolated from any source in Panama, where thousands of people had fallen victims of the disease since the seventeenth century.

Vargas-Mendez and Elton (1953) collected 35 dead monkeys in forests of different areas of Costa Rica during a reported yellow fever outbreak and made a histopathologic diagnosis of the disease in 24 of them, including 14 howlers, 9 red spider monkeys, and 1 squirrel monkey. This became the first time that monkeys were definitely shown to be involved in the natural transmission of jungle yellow fever in Middle America.

Dr. Jorge Boshell, then with the Pan-American Sanitary Bureau, collected several dead howler monkeys in Guatemala and sent five formalinized and 1 glycerinated liver specimens to Gorgas Memorial Laboratory. All five formalinized livers were histopathologically diagnosed as yellow fever and the virus was isolated from the glycerinated specimen. This became the first yellow fever virus isolate obtained from a naturally infected monkey in Middle America (Johnson and Farnsworth, 1956).
Rodaniche and Galindo (1957) isolated yellow fever virus from the mosquitoes *Sabethes chloropterus*, *Haemagogus mesodentatus*, and *H. equinus* collected in Guatemala by Dr. Jorge Boshell, and Galindo et al. (1956) demonstrated experimentally the ability of these mosquitoes to transmit yellow fever virus from monkey to monkey. This work represented the first proof that Central American species of *Haemagogus* were involved in the natural transmission of yellow fever and the first time that a sabethine mosquito was shown to be capable of transmitting the virus through its bite.

Ever since the 1948 outbreak in Panama, scientists of Gorgas Memorial Laboratory have kept up a surveillance for yellow fever activity in eastern Panama. In 1956, while the crest of the wave that gained momentum on the western shores of the canal in 1950 was still killing howlers along the Usumacinta river valley, between Guatemala and Mexico, a new series of events began to take place in Panama. In September 1956 a strain of yellow fever virus was isolated at Gorgas Memorial Laboratory from a pool of *Haemagogus lucifer*. These mosquitoes were collected in the canopy of the forest near Mandinga, on the Atlantic coast of the isthmus, about 25 miles NE of the Pacora woods, theater of the 1948 outbreak. This was followed in October 1956 by the appearance of human cases at the old Pacora site of the 1948 epidemic. Yellow fever virus was also isolated from mosquitoes captured in the canopy of the forest where the human cases had supposedly contracted the disease. The species of mosquitoes involved were: *Haemagogus lucifer*, *H. equinus*, *H. spegazzinii falco*, *Sabethes chloropterus*, and *Anopheles neivai* (Rodaniche et al., 1957). These isolations constituted the first time that yellow fever virus was isolated from any mosquito collected in Panama.

The sequence of events during this outbreak paralleled the timetable of the 1948 epidemic. Following the Pacora flare-up, yellow fever appeared in 1957 on the eastern shores of the Panama Canal, where a human case was diagnosed through isolation of yellow fever virus from its blood and where diurnal arboreal mosquitoes captured in the forest also yielded virus.

In contrast to what occurred during the previous outbreak, when early in 1950 yellow fever crossed to the western shores of the canal, in 1957 the virus failed to cross and faded out of the picture on the eastern shores of the waterway. Trapido and Galindo (1956), who conducted long-term studies on the vector populations in this critical area, have offered an explanation for the usual failure of the yellow fever virus to cross into Central America. These authors believe that conditions around the canal are marginal for sustaining yellow fever transmission, not only because human activity has greatly reduced the acreage of forests, but, more impor-
tant still, because the type of forest covering this area is not conducive to production of high densities of vectors at the usual time that yellow fever virus arrives at the eastern shores of the canal. Therefore, it is only in years of unusually heavy rainfall during this time that conditions become favorable to permit passage of virus into western Panama and Central America.

Galindo and Srihongse (1967), as part of the team of Gorgas Memorial Laboratory scientists who have kept up a long and tedious vigil in the wide expanses of forests of eastern Panama, reported yellow fever activity among the monkey population in the extreme southeastern corner of Darien province during 1965. These same investigators, working in the northern part of the province during 1965 and 1966, failed to find any signs of yellow fever activity in the spiders and howlers of that area and conjectured that an unusually dry year, following the 1965 outbreak, could have disrupted virus transmission by drastically reducing the vector population, thus preventing the formation of one of the typical waves that periodically move westward toward the Panama Canal.

The question as to the origin of the yellow fever waves that from time to time reach the eastern shores of the Panama Canal remains unanswered. Gorgas Memorial Laboratory investigators, working in Darien province since 1958, have failed to find signs of enzootism in this area of eastern Panama, which led Galindo and Rodaniche (1964) to reach the conclusion that yellow fever was neither endemic nor enzootic in eastern Panama, and that the periodic incursions of the virus into this area are probably epizootic extensions of some enzootic center in South America. Kerr (1967) has questioned the validity of this theory with the argument that the negative evidence gathered to date is not sufficient to justify the conclusion arrived at by the above-mentioned authors. Regardless of which side of the question one takes, there is no doubt that somewhere east and south of the Panama Canal the yellow fever virus lurks, hidden in silent transmission cycles, occasionally spilling over into the monkey population and giving rise to the devastating waves of the disease, so well known in the folklore of some areas of tropical America.

B. Experimental Work with Monkeys and Yellow Fever

The classification of New World monkeys is still in a chaotic state and different modern authors disagree extensively as to the names and numbers of families, genera, and species.

For practical purposes we may divide them into six groups, namely, marmosets and tamarins, squirrel monkeys, night monkeys, howlers, spider monkeys, and white-faced monkeys. Susceptibility and tolerance to infec-
tion with the yellow fever virus varies greatly among these groups and even among species of each group. It is, however, difficult to present an accurate comparative picture of the response to the virus of the six groups mentioned above, because of the wide range of susceptibility and tolerance that exists among individuals of one species, as well as between different strains of the virus. In general, all New World monkeys appear to be susceptible to infection with the yellow fever virus and they all seem to circulate enough concentration of virus in the blood to be capable of infecting the mosquito vectors (Bugher, 1951). We may thus conclude that monkeys play a major role in sustaining the natural transmission chain of jungle yellow fever in the American tropics. Comparative estimates of susceptibility and tolerance to yellow fever infection in six groups of New World monkeys are presented in Table I. It must be borne in mind that these are gross estimates, subject to limitations imposed by the variabilities noted previously and based, in part, on inconclusive experimental work. The table will be useful, however, in interpreting basic points on the ecology of jungle yellow fever in Middle America. Following is a presentation of the salient points of laboratory research with yellow fever virus and each of the groups of monkeys mentioned above.

1. Howlers

These monkeys belong in a single genus, *Alouatta*, as generally accepted by all modern mammalogists. Speciation in the group is still not well understood and there is general disagreement as to the names that should be applied to the different populations of howlers that extend from Mexico south to Argentina and Bolivia.

Little experimentation has been carried out on the susceptibility of howlers to the yellow fever virus, because of the difficulties experienced.

<table>
<thead>
<tr>
<th>Monkeys</th>
<th>Susceptibility to infection</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howlers</td>
<td>Very high</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>Marmosets</td>
<td>Very high</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>Squirrel monkeys</td>
<td>Very high</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>Night monkeys</td>
<td>Very high</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Spider monkeys</td>
<td>High</td>
<td>Moderate-to-low</td>
<td>Moderate-to-low</td>
</tr>
<tr>
<td>White-faced</td>
<td>Probably moderate</td>
<td>Low-to-negative</td>
<td>Low-to-negative</td>
</tr>
<tr>
<td>monkeys</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
everywhere in keeping them alive under laboratory conditions. Davis (1931) infected a single specimen of the red howler by mosquito bite and was able to recover virus by blood transfusion to a rhesus monkey and by feeding *Aedes aegypti* mosquitoes on its blood. Laemmert and Kumm (1950), working with the howler *A. caraya*, were successful in carrying on several cyclic transmissions from monkey to mosquito to monkey, using two forest mosquitoes of Brazil, namely, *Aedes leucocelaenus* and *A. scapularis*. Results of large-scale neutralization tests for yellow fever immunity among natural populations of howlers of Mexico, Central America, Panama, Trinidad, and South America indicate that howlers frequently become infected in nature with the virus.

2. **Marmosets and Tamarins**

These primates belong to some six genera of the family Calithricidae and extend from Panama to southern Brazil. A great deal of experimental work has been carried out with marmosets and yellow fever and all species have been shown to be extremely susceptible to infection, with development of severe illness and high mortality. In some regions of South America they have been shown to be important as links in the transmission chain of the virus. However, the only species known from Panama does not appear to play an important role in yellow fever transmission, as it seldom comes in contact with the vectors, because it is mainly an inhabitant of second-growth forests which do not sustain high population densities of the natural vectors of the disease.

3. **Squirrel Monkeys**

There is but a single recognized species, namely, *Saimiri sciurius*, known from Venezuela, the Guianas, the Amazon area of Brazil, Colombia, the Pacific coast of western Panama, and adjacent areas in Costa Rica. This monkey is extremely susceptible to infection and capable of sustaining yellow fever transmission through many monkey-mosquito-monkey passages. They usually develop severe symptoms of the disease and often die of it. Because of its restricted distribution, it can only be considered as locally important in the natural transmission of yellow fever. In Panama and Costa Rica it may have played a very important role in an outbreak which became localized in its area of distribution within these countries.

4. **Night Monkeys**

A single species is recognized today, *Aotus trivirgatus*, which extends from eastern Panama south to the Orinoco and Amazon basins. The species is nocturnal, sleeping during the day in well-protected tree holes. It is extremely susceptible to infection with yellow fever, circulates high
concentrations of virus in the blood, being capable of infecting vector mosquitoes. It is affected by the virus with severe illness which is frequently fatal. Because of its restricted distribution and its habits, which keep it away from the diurnal vectors, the species does not seem to be very important in sustaining transmission cycles of yellow fever in nature.

5. Spider Monkeys

These monkeys belong to the single genus *Ateles*. There are several species which extend from Mexico south to Brazil. Experimental work carried on by Davis (1930a) with *A. ater* (= *A. paniscus*) and by Galindo et al. (1956) with *A. fusciceps*, the black spider monkeys of Brazil and Panama, respectively, has shown that they are highly susceptible to infection and are capable of infecting natural vectors. *Ateles fusciceps*, the black spider of eastern Panama, tolerates yellow fever infections well, developing light-to-moderate symptoms but seldom dying of the disease.

6. White-faced Monkeys

All the white-faced or capuchin monkeys belong to the genus *Cebus*, which has been divided into many species, extending its range from Honduras south to Brazil and Peru. Experimental work by Aragao (1928) and Davis (1930b, 1931), with several strains of yellow fever, has demonstrated that capuchin monkeys are susceptible to the virus and are capable of infecting mosquito vectors. However, infections are usually asymptomatic and very seldom fatal.

C. FIELD OBSERVATIONS ON MONKEYS AND YELLOW FEVER

The massive experimental data accumulated on the susceptibility and tolerance of New World monkeys to the yellow fever virus, summarized above, have been amply confirmed by field observations.

The susceptibility to yellow fever infection and high morbidity and mortality in howlers, demonstrated in the few laboratory experiments carried out with them, has been amply corroborated in the field by the incredible mortality of these monkeys observed during jungle yellow fever outbreaks in Central America and Trinidad. It has been demonstrated in these areas that howlers are extremely sensitive indicators of the presence of yellow fever virus. When howlers cease to be heard in the forest, or when groups of them are found dead of natural causes, there is a good likelihood that human cases of yellow fever will soon begin to appear. Stories of the “silence of approaching death” are commonly picked up by scientists from country folk of Trinidad, Guatemala, Nicaragua, and parts of Brazil, who live in intimate contact with the forest. They tell of the
Yellow Scourge sweeping through the countryside soon after the booming calls of the howlers, that always fill the morning air as dawn breaks over the tropical rain forest, are suddenly replaced by an ominous silence, which they consider a presage of imminent tragedy. The vivid accounts given by Dr. Jorge Boshell of his trips through the Central American jungles during yellow fever outbreaks, when he observed literally hundreds of howler monkeys falling out of trees like rotten fruit, constitute an unforgettable experience for those of us fortunate to have heard them firsthand.

Field observations on spider monkeys and yellow fever do not fall in the same pattern as that described for howlers. There are two species of spider monkeys in Central America which appear to have played important roles in maintaining the transmission chain of jungle yellow fever in the forest: the black spider of eastern Panama and the red spider of Western Panama and Central America. When human cases of yellow fever appeared near Almirante, in extreme northwestern Panama during 1951, they were preceded by unusual mortality of red spiders in the mountains to the southwest of Almirante, reported by an engineer in charge of a road-surveying crew. It is interesting to note that the first yellow fever case diagnosed in Almirante, which resulted in death was that of a member of this crew. The story of how this man died of yellow fever, after being vaccinated a few days too late, is one example of the many tragic incidents that occurred as Yellow Jack moved relentlessly north through the Central American forests.

One day in April 1951, the engineer and two of his chainmen were walking across the continental divide from Chiriquí to Bocas del Toro and came to rest at noon by a stream, under the branches of a huge almendro tree whose fruit is a favorite food of spider monkeys. He noted many “blue mosquitos” biting them at the edge of the clearing in the forest made by the stream and also was puzzled by finding, under the same almendro tree, about a dozen fresh cadavers of red spider monkeys which appeared to have died of natural causes. Next day he arrived at Almirante and immediately took a plane bound for Panama City, where he related his findings to Gorgas Memorial Laboratory scientists. Upon being told that the monkeys had probably died of yellow fever and that he and his men should be immediately vaccinated, he returned to Almirante the following day. It took him all of 24 hr to round up his men and take them to the Almirante hospital where they received the yellow fever vaccine in the morning. The crew walked back a few hours later to their jungle camp located some 12 km from Almirante. That evening one of the chainmen, who had accompanied the engineer across the mountains, came down with chills and fever and by the next day he was jaundiced and had developed the dreaded “coffee-colored vomit.” He was carried to the
Almirante hospital where he died a few days later. A piece of his liver removed at autopsy showed the typical pathologic lesions of yellow fever.

As this epidemic wave moved through Costa Rica and Nicaragua, Vargas-Mendez and Elton (1952) and later Boshell (1952) picked up a number of dead red spiders in the forest whose cause of death was histopathologically diagnosed as yellow fever. During a visit to Chontales province in Nicaragua by Boshell, Trapido, and Galindo (Trapido and Galindo, 1956), immediately after the epidemic wave of yellow fever had passed through the area, observations were made on the populations of howlers, red spiders, and white-faced monkeys which occur in the area. Natives reported finding huge numbers of howlers, some red spiders, but no white-faced monkeys dead in the forest. The scientists neither saw nor heard howlers, but ran across small groups of red spiders and large bands of white-faced monkeys. These observations fit the general tolerance picture among these monkeys given in Table I. It is clear from these accounts that red spider monkeys frequently die of yellow fever infection during outbreaks. However, in general, the species appears to be more tolerant of the virus than the howler, as a good number of them survive the infection and develop permanent immunity against the disease.

The black spider monkey of Panama does not react to yellow fever in the same manner as its kin from Central America. Laboratory experiments carried out at Gorgas Memorial Laboratory have demonstrated that black spiders seldom perish as the result of the disease. Observations carried out in the forests of eastern Panama, after yellow fever has swept through them, also show the great tolerance of the black spider to the virus, as populations of this primate do not appear to be affected at all.

D. Monkeys in the Detection of Jungle Yellow Fever

Gorgas Memorial Laboratory has been interested in studying the ecology of yellow fever in eastern Panama, as a means to elucidate the origin of the epidemic waves which periodically move from east to west across the isthmus. Through these studies, it has been possible to detect two such waves that made their appearance after the rediscovery of yellow fever in Panama in 1948. The existence of one was demonstrated in the Pacora area in 1956, and the second one was discovered in Darien in 1965.

Detecting activity of jungle yellow fever in the virgin forests of eastern Panama is a difficult task at best. There are no human inhabitants in these forests and the few Indians and Negroes that venture into them are immune to yellow fever, so that attempts to diagnose the presence of the disease by picking up human cases, through viscerotomy or other means, do not offer good possibilities of success. The finding of dead howlers in
these forests is far less feasible than in other areas, because the frequent waves of yellow fever that pass through keep the growth of howler populations under restraint. For this reason, during outbreaks in these sparsely inhabited wide expanses of forest, there have been no reports of dead howlers. However, in studying populations of this species of monkey before and after yellow fever episodes, it has been noted that individual groups of this highly gregarious animal are drastically reduced in numbers. Since howlers are easy to locate because of the noisy calls of males, a few weeks spent in a particular forest may serve to estimate the average size of howler groups and determine whether they are normal or greatly reduced in numbers. In this way, useful information may be obtained as to possible recent yellow fever activity.

Black spider monkey populations are not affected during yellow fever outbreaks, so population densities offer no information as to possible recent activity of yellow fever in an area. It is known, however, that black spiders are quite susceptible to infection with the yellow fever virus and that they develop permanent immunity to the virus soon after infection. By bleeding and testing a sample of the black spider population of a particular forest, and determining the approximate age of each specimen bled, it becomes possible to arrive at a reasonable conclusion regarding recent jungle yellow fever activity. In areas of eastern Panama that have just been visited by jungle yellow fever, a high percentage of the spider monkey population will be found to have immune antibodies in the blood, with many positive samples among young specimens. In areas not recently affected by a yellow fever wave, the rate of individuals with antibodies will be much lower, with no positives among the younger age groups. While white-faced monkeys do not seem to be affected by yellow fever, they are not as good indicators of jungle yellow fever activity as the black spiders, since they appear to be somewhat more refractory to infection in eastern Panama, as shown by the significantly lower antibody rates found in the white-faced monkeys.

Another successful method of detecting the presence of yellow fever virus is through the use of sentinel monkeys. There are two ways by which monkeys may be used as sentinels. One is by exposing them in the canopy of the forest continuously and checking them daily for development of symptoms. Another is by direct inoculation into them of the blood of wild-caught monkeys. Rhesus monkeys were widely used at first as sentinels because of their high susceptibility to the virus, but in later years they have been replaced by native American species, such as spider monkeys, which are more gentle and easier to handle in the field.

These methods of field observations, blood-testing of the wild primate populations and exposure of sentinel monkeys for detecting waves of jungle
yellow fever in eastern Panama, are the methods of choice utilized by Gorgas Memorial Laboratory in yellow fever surveillance activities being developed in Darien province. They are extremely useful, as they yield information regarding movements of yellow fever waves from east to west, much before arrival of the virus at densely populated centers in the general vicinity of the Panama Canal.

III. Monkeys and Yellow Fever in the Future

In this chapter we have attempted to present a concise summary of the role that the monkey has played in yellow fever research. This disease, which has plagued the world for many centuries, will continue to haunt the tropics as long as wide expanses of forests remain standing. The monkeys, in their role as amplifiers of the yellow fever virus, will also continue to be a threat to the health of human beings dedicated to the conquest of this disease of the tropics. However, through the efforts of countless men of science, which we have attempted to summarize above, these same monkeys have now become useful tools in the hands of scientists to help detect approaching danger, when silent yellow fever waves slowly move through uninhabited forests and creep up on areas densely populated by susceptible human beings. These warning signals offered by monkeys, will allow public health authorities to initiate intense vaccination campaigns before arrival of the wave, thus saving many human lives that would otherwise have fallen victims to the Black Vomit.

In summary, monkeys were important in the experiments that were concerned with the following: the discovery of the virus of yellow fever; the first transmission of the virus to a nonhuman animal; the production of the first vaccine; and the elucidation of the differences between urban and jungle types of the disease. Monkeys are the major reservoirs of jungle yellow fever. Also, they are now being used in surveillance for yellow fever in the Panama jungles, to warn public health authorities of the approaching danger to densely populated centers around the Panama Canal.

Yellow fever is only one of some hundreds of viruses. As with yellow fever, many of these viruses are known to be, and others will be shown to be, common pathogens of man and monkey. The important part played by the monkeys in the yellow fever work presages their possible greater role in studying other viral agents in the future.

REFERENCES