

Yellow Fever: History and Disease

The Challenge of Yellow Fever

Diseases, including yellow fever, killed more men in the Spanish-American War than did the enemy. Yellow fever may have first appeared in Central America in 1596, probably imported from Africa by slave ships. It may have been the disease from which members of Columbus' second expedition suffered in 1495. Ninety epidemics struck the United States between 1596 and 1900. In 1793 an epidemic first hit Philadelphia, then the U.S. capital, causing the Government to flee as ten per cent of the population perished. Washington went to Mount Vernon while Jefferson fled the disorder caused by the onslaught of the disease. Because of frequent epidemics, which destroyed ninety per cent of his expeditionary forces in 1802, Napoleon was influenced to sell the Louisiana Territory. It was chiefly because of malaria and "yellow jack," as the disease was nicknamed from the pennant which was flown during quarantine, that the French were unable to complete the Panama Canal. The danger of contaminating the southern states was considered to be a major factor in the annexation of Cuba.

The onset of yellow fever came with chills and a headache. Then followed severe pains in the back, arms and legs accompanied by high fever and vomiting. The feverish stage might last hours, days, or weeks. Jaundice, from which the fever derives its name, might then appear. Then came the so-called "stage of calm" when the severity of the symptoms subsided and the fever dropped. In less serious cases this stage indicated recovery. But in the main, this stage was followed by a return of the fever accompanied by internal bleeding which caused the dreaded "black vomit" when blood released into the stomach was ejected. Reed and Carroll had estimated that there were 300,000 cases in the United States between 1793 and 1900, which cost the nation almost \$500,000,000 with a mortality rate usually at forty per cent but sometimes as high as eighty five per cent. The scourge of yellow fever had plagued the southeastern United States for almost two hundred years, but nowhere was it more prevalent than in Havana.

Following the end of the Spanish-American War, yellow fever loomed as a significant problem for the U.S. Army during its planned four year occupation of Cuba. In 1899, Reed and his assistant James Carroll published a paper refuting the claim of the respected Italian scientist Guiseppe Sanarelli that a bacterium he had discovered was the agent of yellow fever. Surgeon General Sternberg, the country's leading expert on yellow fever, agreed with them completely. In the late spring of 1900, as the yellow fever season approached and the sanitary measures taken to protect the forces in Cuba were clearly less than adequate, Sternberg appointed a group of Army physicians to study the issue in Cuba.

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The Commission then decided that the best way to approach yellow fever was not by searching for a specific agent but rather by identifying the means by which the fever was transmitted. They turned their attention to the theory of Dr. Carlos Juan Finlay and examined it more carefully. For nineteen years this resident of Havana had contended that yellow fever was carried in the body of a common house mosquito which at that time was called *Culex fasciatus*, later *Stegomyia fasciata*, and is now known as *Aedes aegypti*. This theory had been expounded even earlier, but it was Finlay who was its staunchest exponent. However, after some 100 experimental inoculations had failed to produce any clear cases of the disease under strict laboratory control, Finlay was scoffed at; people referred to him as the "mosquito man." There was evidence, however, that tended to lend credence to this theory, which even the Yellow Fever Commission, optimistic though it was, had doubted. First of all, the disease skipped erratically from house to house, jumping around corners. One member of a household might contract the disease while others in close contact never became ill or did so after a period of about two weeks had elapsed. This was quite unlike any other infectious disease except malaria, which had just recently been shown by Major Ronald Ross of the British Army to be spread by the *Anopheles* mosquito.

Disease Studies Begin

On June 25, 1900 Walter Reed arrived at Columbia Barracks in Quemados about six miles from Havana. Major Reed visited the hospital where his friend Major Jefferson R. Kean, Chief Surgeon of the Department of Western Cuba, was ill with yellow fever. It was the first active case Reed had ever seen, fortunately Kean recovered. Despite the fact that Reed and Carroll had published results contrary to it, the Commission members set out to see if they could validate Sanarelli's theory. By August, 1900, however, they had found no causal relationship between *Bacillus icteroides* and yellow fever. *Bacillus icteroides* was actually a member of the hog-cholera group.

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Reed Returns to Washington

Although Major Reed was called back to Washington to finish the Typhoid Commission report following the unexpected death of one of its members, the work of the Yellow Fever Commission went forward. Dr. Lazear had recently been working with malarial mosquitoes and attacked his duties with great enthusiasm in view of the information he had concerning the observations of Dr. Henry R. Carter of the Marine Hospital Service (now the Public Health Service). Dr. Carter, who was assigned in Cuba at the time, had observed that it took two or three weeks for the first case of yellow fever to produce the next case in a community. On the basis of this observation, he suspected that an insect might be the intermediary since this would account for the delay in transmission. He called this the "extrinsic incubation period."

Dr. Finlay had given some of the black, cigar-shaped eggs to the Commission, and Lazear allowed them to hatch. In the warm summer months, it was not difficult to maintain a supply since the mosquitoes bred in any clean, still water. Several members of the research team (including Drs. Carroll and Lazear) then volunteered to be bitten but initially without producing illness. Later Carroll was bitten again and promptly developed a successful case of yellow fever but his case was experimentally defective since there may have been other sources of contamination. Despite a very severe case, Carroll fortunately recovered and went on with his work in bacteriology. Next, Lazear asked Private William Dean of Ohio if he would consent to be bitten. Answering that he wasn't "afraid of any little old gnat" Dean permitted the female *Aedes aegypti* to dine on him. He developed the first unquestionable experimental case. Dean survived.

Dr. Lazear Dies, Reed Rejoins the Study

Dr. Lazear himself came down with yellow fever and tragically died after several days of delirium and black vomit - a true martyr to science. The exact details of how he acquired his illness will probably never be known, as he had several possible exposures, including possibly from self-experimentation.

With the Typhoid Report completed and word of Lazear's death, Major Reed quickly returned to Cuba. Although grieved at Lazear's death, he was excited at the prospect of successfully tracking down the secret of the fever. Dr. Lazear's notebook, found by Lieutenant Albert E. Truby, yielded the key. In it, through the carefully recorded controlled experiments, Walter Reed found that in order for a mosquito to become infected, it had to bite a yellow fever patient during the first three days of his illness; only during

that time was the agent present in the bloodstream. Further, it required at least twelve days for the agent to incubate in the female mosquito (only the female aegypti draws blood) before the fever could be passed to another person.

Progress Announced

In October 1900, Major Reed was able to announce to the annual meeting of the American Public Health Association that "the mosquito serves as the intermediate host for the parasite of yellow fever." These two cases, although sufficient to convince the Yellow Fever Commission that they were at last experiencing some success, were not enough for the thorough scientific mind of Walter Reed, nor would they be for a public that the press had instructed in the "foolishness" of the mosquito theory. With the express permission and financial support of General Leonard Wood, Governor General of Cuba, Camp Lazear, named for their fallen comrade, became operational on November 20, 1900.

Human Volunteers Begin Participation in Yellow Fever Study

Dr. Carroll had exhausted the list of experimental animals, rats and the like normally used for scientific research, failing to find any susceptible to yellow fever. Human volunteers would be needed. General Wood also authorized the Commission to use and pay American and Spanish volunteers to participate in the experiments.

Reed Proves Method of Transmission

In addition to the mosquito theory, Dr. Reed also desired to disprove the seemingly fallacious belief that yellow fever could be transmitted and induced from clothing and bedding soiled by the body fluids and excrement of yellow fever sufferers. These articles were known as fomites and were commonly thought to carry the disease. Just as "everybody knew" that the mosquito theory was foolish, so "everybody