The Unsung Hero of Yellow Fever?

Historians dispute a new book claiming that Jesse Lazear, not Walter Reed, deserves credit for discovering that yellow fever is spread by mosquitoes

Ever since the turn of the century, Walter Reed has been known as the man who conquered yellow fever. With a series of experiments performed in 1900, he proved that yellow fever is transmitted by mosquitoes, a finding that quickly led to control of the dread disease in North America and permitted construction of the Panama Canal in a region that had formerly been a graveyard for visiting Americans and Europeans. But a new book, published on 28 March, attempts to demolish the Walter Reed legend, claiming that Reed took credit for work performed by a junior colleague who experimented on himself and died as a result (*1*).

Thanks in part to a provocative press release, in which one of the authors suggests that the name of the Walter Reed Army Hospital should be changed, the book is receiving considerable popular attention. Among medical historians, however, it has not gone down too well. "They are quite wrong," says William Bean, whose own biography of Walter Reed (*2*), published last year, presents a very different account of Reed's yellow fever work.

Jon Franklin, a medical writer for the Baltimore *Sun*, and John Sutherland, a pathologist at the University of Maryland, claim in *Guinea Pig Doctors* that credit for the key breakthrough in the yellow fever work should go to Reed's junior colleague, Jesse Lazear, who was in Cuba conducting experiments while Reed was in the United States. Lazear managed to infect human volunteers—including himself, the book claims—by bites from contaminated mosquitoes. It was the first time yellow fever had been transmitted experimentally. Reed, according to Franklin and Sutherland, did not believe the mosquito theory until he read details of the experiments in his dead colleague's notebook. He promptly reported the findings without giving Lazear full credit for the discovery.

The book reconstructs in "docu-drama" style the stories of eight physicians who experimented on themselves. Although the Jesse Lazear story takes up only one chapter, it is by far the most controversial, and the controversy is compounded by the fact that Franklin and Sutherland provide no sources for their information. It is thus sometimes difficult to tell where established fact ends and imaginative reconstruction begins.

Franklin says they first tried to tell the story of Lazear in the conventional way, depicting him as just a part of Reed's research team, but "it just didn't seem to make sense." The more they looked into Lazear's role the more crucial it seemed, he says. Sutherland admits they did not do any original research on documents from the period, but relied for some key information on a paper published in 1971 in the alumni magazine of Lazear's alma mater, Columbia University College of Physicians and Surgeons (*3*).

There has, in fact, always been some mystery attached to Lazear's experiments because several contemporary accounts of them are wildly contradictory and the key document—Lazear's notebook—is missing. Bean believes it was stolen from Reed's desk when he died in 1902. All the accounts agree that Lazear successfully transmitted the disease to two volunteers—James Carroll, a physician who was also working with Reed on yellow fever, and William Dean, an Army private—but they differ chiefly on whether Lazear's fatal bout with the disease was the result of self-experimentation or an accidental bite from an infected mosquito.

There is, however, no doubt that Lazear's notebook provided the crucial information for Reed's first published paper implicating mosquitoes in the transmission of yellow fever. (Lazear, Carroll, and Aristides Agramonte, the fourth member of Reed's yellow fever research team, are listed as coauthors of the paper.) This is the central point in Franklin and Sutherland's attack. But others argue that Reed, as head of the research team, helped plan the experiments, and they maintain that Reed deserves particular credit for a subsequent set of experiments in which he proved that all other routes of infection could be ruled out. "Reed's genius was in setting up [that] controlled experiment," says Robert Joy of the Uniformed Services University of the Health Sciences in Bethesda, Maryland. "But you can't design great experiments until you have a brilliant breakthrough," responds Sutherland.

At the time Reed's research team was conducting these studies, yellow fever was perhaps the most feared disease in the Western Hemisphere. Endemic in much of South and Central America, it would periodically break out in the southern United States, also ravaging cities as far north as Boston and killing up to 20 percent of its victims. It was widely believed to be spread through contact with infected articles such as clothing, a belief that prompted strict quarantine and fumigation of potentially contaminated material.

Although typhoid fever claimed more lives, yellow fever struck more dread because of the unpredictability of the epidemics and the frightful nature of the disease. It was marked by high fever,

Photos by National Library of Medicine

A painting depicts Walter Reed (center) watching while Jesse Lazear applies a mosquito to the arm of James Carroll. In fact, Reed was in Washington when Lazear did this experiment. Behind Lazear are Carlos Finlay, who originated the mosquito theory, and Aristides Agramonte, the fourth member of the yellow fever board.

jaundice, bleeding from the mouth and gums, and, finally, kidney failure. The disease took a week or so to run its course; those who survived were rendered immune to subsequent infection.

Reed first became deeply involved in yellow fever research in 1897, when he was a 46-year-old surgeon who had had a relatively unremarkable career in the Army Medical Corps. He was set to work investigating a bacillus that an Italian scientist, Giuseppe Sanarelli, claimed to have isolated from yellow fever patients. Reed soon concluded that Sanarelli's putative yellow fever agent was in fact a hog-cholera bacillus.

While this scientific digression was taking place, a medical disaster was under way in U.S. Army camps. Troops who had enlisted to fight in the 1898 war with Spain were dropping like flies from disease, chiefly typhoid fever. Reed was appointed by Surgeon General George Sternberg to lead an investigation. His work, now considered a classic of epidemiology, helped pinpoint the cause of typhoid fever and led to a major sanitation effort by the Army Medical Corps.

There was every expectation that the clean up would also take care of yellow fever among troops stationed in Cuba after the war. But when the rainy season began in the spring of 1900, yellow fever struck again with a vengeance. Faced with a major calamity, Sternberg dispatched Reed to Cuba to head a four-member board to investigate the causes of the disease. The other members were Reed's longtime associate James Carroll, Jesse Lazear, and Aristides Agramonte. Lazear and Agramonte were already in Cuba working as Army contract surgeons.

Reed and Carroll arrived in Cuba in June 1900 and the board immediately set to work looking for organisms in the blood of yellow fever victims. They looked especially for Sanarelli's bacillus, for in spite of Reed's earlier work, Sanarelli's claims were still getting a lot of attention. The board drew a blank, which upheld Reed's findings but got them no nearer a solution.

In spite of the evident failure of sanitation measures to curb yellow fever, virtually everybody was still convinced that it was a contagious disease. Nobody much gave credence to an alternative hypothesis first proposed nearly two decades previously by a Cuban physician, Carlos Finlay. Finlay argued that the disease was spread by mosquitoes, and with a piece of brilliant deduction, he singled out the common household mosquito *Culex fasciatus*—now known as *Aedes aegypti*—as the culprit. He continued to hold tenaciously to his theory even though he was unsuccessful in many attempts to transmit the disease with mosquitoes that had bitten yellow fever patients.

In the waning years of the 19th century, two pieces of research provided at least some theoretical credibility for Finlay's ideas. The first was the publication in December 1897 of a paper by a British physician, Ronald Ross, demonstrating that the malarial parasite is transmitted by the *Anopheles* mosquito after a period of incubation in the insect's abdomen. Ross's work electrified the world of tropical medicine, and Lazear, who was then working at Johns Hopkins University, was one of the first researchers in the United States to confirm his findings.

The second important pointer came from an elegant epidemiological study by Henry Rose Carter of yellow fever in two small Mississippi towns. Carter noted that an outbreak would usually begin with a single case, usually a person who had returned from an infected city such as New Orleans, then there would be a gap of 2 to 3 weeks before new cases would arise. Carter called this the "extrinsic incubation" period. Carter was in Cuba when Reed arrived and discussed his findings with him. Then, on 26 June 1900, Carter sent a note to Lazear suggesting that "the a priori argument for Dr. F's [Finlay's] theory has much in its favor." Reed would later write to Carter that "your own work in Mississippi did more to impress me with the importance of an intermediate host than everything else put together."

In any case, having made no progress in its search for a yellow fever organism, the Reed commission decided to investigate Finlay's theory. Because of his earlier work on the malarial parasite, Lazear was put in charge of the mosquito work, while Carroll and Agramonte continued with their bacteriological studies.

An Ineradicable Disease

When the Reed board proved that yellow fever is transmitted by the urban mosquito *Aedes aegypti*, victory over the disease seemed to be in sight. A massive mosquito control program virtually eliminated yellow fever from the United States and Cuba in the early 1900's and removed the single largest obstacle to construction of the Panama Canal. Buoyed by this success, there was hope that the disease could be eradicated entirely from its traditional haunts in South America and Africa. (Yellow fever has never appeared in Asia, although *Aedes aegypti* are common there.) But total eradication turned out to be impossible.

In the 1930's, it was discovered that South American and African monkeys harbor the disease and that the virus is transmitted among them by mosquitoes that live in the forest canopies. Occasionally, yellow fever will be transmitted from this jungle cycle to humans. There is thus an ineradicable reservoir and an ineradicable vector for the disease. Moreover, unlike smallpox, which only infects humans, yellow fever can never be eliminated by a widespread vaccination campaign. A live-virus vaccine developed in the 1930's—and still used today—does, however, provide solid immunity.

According to a recent report by the U.S. Centers for Disease Control, some 200 to 300 cases of yellow fever are reported each year in South America, and in Africa "epidemics involving forest mosquito vectors affect tens of thousands of persons at intervals of a few years, but few cases are officially reported."

One potentially worrying development is that *Aedes aegypti* control programs virtually ended in the late 1960's and the mosquito is now firmly reestablished in South America, the Carribbean, and parts of the United States. One measure of its resurgence is the spread of dengue fever, which is also transmitted by *Aedes aegypti*. Only a handful of cases of dengue fever were reported in the Carribben nations in the 1960's, but epidemics of the disease are now occurring virtually every year in the region.

This combination of a reservoir of yellow fever virus in the South American rain forests and a resurgence of *Aedes aegypti* in the urban areas is a cause for concern. Some public health specialists believe it will be only a matter of time before a person infected in the forest touches off an urban outbreak of the disease.—**C.N.**

The board paid Finlay a visit at his home in Havana, and he gladly gave them some *Aedes aegypti* eggs.

Because no animals were known to be susceptible to the disease, the only way to test Finlay's ideas was to experiment on human volunteers. Reed, Carroll, and Lazear agreed to be among them. (Agramonte, who was born in Cuba, was assumed to be immune as a result of early childhood infection.) Before the experiments got under way, however, Reed was called back to Washington in early August by Sternberg to complete the report on typhoid fever that he had begun before he was sent to Cuba.

Lazear hatched the mosquito eggs and kept each insect in a glass tube. By unstoppering the tubes and inverting them over the skin of yellow fever patients, he coaxed the mosquitoes to feed on supposedly contaminated blood. After a few days, he let them bite healthy volunteers, including himself. Nothing happened. Writing 15 years later (*4*), Agramonte recalled that after these early failures, "even members of the board, who were rather sanguine in their early expectations, became somewhat discouraged," and "the most enthusiastic, Dr. Lazear himself, was almost ready to 'throw up the sponge.' "

But Lazear persisted. On 27 August, he applied a mosquito that had bitten a yellow fever patient 12 days earlier to the skin of his colleague, James Carroll. A few days later, Carroll came down with a severe case of yellow fever that nearly killed him. Although Lazear and Agramonte were convinced that Carroll was infected by the mosquito bite, they could not rule out an alternative route of infection because Carroll had been in yellow fever wards and even in the autopsy room a few days before falling ill.

They had a much more convincing case a few days later, however, when a volunteer soldier, William Dean, fell ill after being bitten by Lazear's mosquitoes. Dean had been nowhere near yellow fever patients for almost 2 months.

The sweetness of this success quickly turned sour, however, when Lazear himself became ill on 18 September and died a week later after going through some of yellow fever's worst agonies. How he contracted the disease remains a mystery.

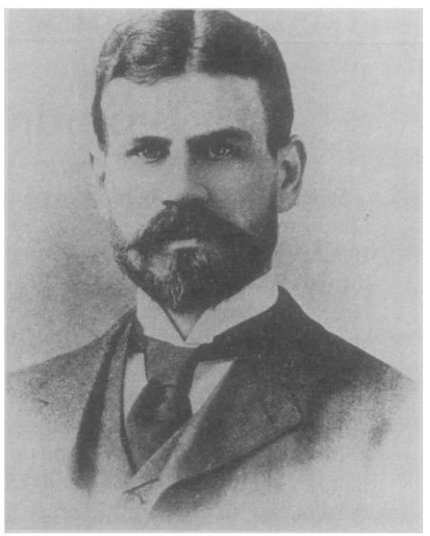
Agramonte and Carroll both recalled that Lazear told them in his lucid moments that he had been bitten on the hand by an unidentified mosquito while trying to coax one of his own insects to feed on the blood of a yellow fever patient. But Albert Truby, who was attached to the military hospital in Cuba at the time, wrote in a biography of Walter Reed 40 years later (*5*) that "all of us at the hospital were convinced that Lazear had placed the mosquitoes on his own arm." Truby speculates that Lazear's colleagues kept his self-experimentation quiet because his death could have been ruled a suicide, thereby depriving his wife of insurance benefits.

Franklin and Sutherland reconstruct the events without even a hint of doubt:

> Jesse reached for a test tube, checked its label, and made an entry in the brown notebook. . . . He looked up at the mosquito, thinking. Then he picked up the vial, uncapped it, and held its open end against his skin.

Lazear's pocket notebook, in which he carefully recorded the details of his experiments, could presumably clear up the mystery of his own infection, but it has not been seen since Reed died of appendicitis in 1902.

Reed hurried back to Cuba, arriving on 3 October, and began what Truby described as a "whirlwind of activity." Lazear's notebook evidently contained an important clue: the mosquitoes that had bitten Carroll and Dean had fed on yellow fever patients at least 12 days previously, thus corroborating Carter's observations about a period of extrinsic incubation. Reed put together a paper, which he delivered at a meeting of the American Public Health Association in Indianapolis on 23 October (*6*).



Jesse Lazear

Conducted the early experiments.

Walter Reed

Carried out a controlled study.

Although Franklin and Sutherland accuse Reed of stealing all the credit, the paper was presented as a joint report of the yellow fever board, with all four members listed as coauthors. Carter and Finlay were also given full credit for steering the board toward the mosquito theory. Franklin and Sutherland imply that Reed gave Finlay no credit at all.

The findings were immediately challenged because they scarcely amounted to definitive proof, and within a month Reed was back in Cuba planning an ingenious set of experiments in which paid volunteers were subjected to various potential routes of infection. Only those bitten by contaminated mosquitoes came down with the disease; none died. A report of the experiments, published in the 16 February 1901 issue of the *Journal of the American Medical Association* (*7*), provided the convincing proof.

Lazear clearly played a key role in a discovery for which Reed is popularly remembered. But Reed's contribution was far from negligible, contrary to what Franklin and Sutherland imply. "There is plenty of credit to go around for everybody, without taking anything away from Reed," maintains Reed's biographer Bean.—**COLIN NORMAN**

References and Notes

1. J. Franklin and J. Sutherland, *Guinea Pig Doctors* (Morrow, New York, 1984).
2. W. Bean, *Walter Reed* (University Press of Virginia, Charlottesville, 1982).
3. J. A. del Regato, *P & S Quarterly* (fall 1971).
4. Agramonte's account was published in *Scientific Monthly*, December 1915. It is reprinted in full in B. G. Rosenkrantz, Ed., *Yellow Fever Studies* (Arno Press, New York, 1977).
5. A. E. Truby, *Memoir of Walter Reed* (Hoeber, New York, 1943).
6. Lazear's notes contained a second clue that Reed apparently missed at the time: the mosquitoes that bit Carroll and Dean had bitten yellow fever patients in the early stages of their disease. It is now known that the mosquito can pick up the virus only in the first 3 days of infection, and that at least 12 days must elapse before the mosquito can pass it on. The paper was published in *The Philadelphia Medical Journal* (1900), vol. 6, p. 790; it was reprinted in *Reviews of Infectious Diseases*, vol. 5, No. 6, November–December 1983.
7. W. Reed, J. Carroll, A. Agramonte, "The etiology of yellow fever: An additional note, *Journal of the American Medical Association*, 16 February 1901, p. 431; it was reprinted in *ibid.*, 5 August 1983, p. 649. The paper also contained the important information that yellow fever could be transmitted by injections of blood taken from a patient with the early stages of the disease.