

# Virtual Mentor

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## HISTORY OF MEDICINE

### Politics of Participation: Walter Reed's Yellow-Fever Experiments

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At the termination of the Spanish-American War in 1900, American military forces occupied the island of Cuba. Tropical diseases were a major concern of the government, and the American Surgeon General dispatched Major Walter Reed and a team of young doctors to investigate the diseases, particularly the pathogenic mechanism of yellow fever. Reed's team pursued a program of human experimentation by intentionally exposing human subjects, team members included, to potentially deadly virulent material. Despite several prominent fatalities during the experiment's run, Reed's experiments were a scientific success and instrumental in establishing that yellow fever was a mosquito-borne illness. Mosquito-control initiatives based on the findings were remarkably successful and began to reduce the incidence of the violent hemorrhagic fever significantly. For years following the experiments, the honor, bravery, and heroism of the volunteers were extensively celebrated in publicity campaigns, charity drives, a government-published "Yellow Fever Roll of Honor," popular books, a movie, and a Broadway play.

The abundant memorializing often assumed that heroism and bravery were the primary motivations of those who participated in the experiments. In looking at this piece of history, I seek to examine the question of motivation, using primary materials collected by the physician-historian Philip S. Hench in the 1940s, including first-person interviews with some of the surviving ex-volunteers. The analysis reveals that the actual self-stated motives for participation were more complex than simple honor or bravery; other factors such as ignorance of the risks, professional and occupational self-interest, and monetary inducements were pivotal. Moreover, as the experiments evolved in protocol and design, so too did subjects' assessments about the potential risks and rewards of participation. While honor and bravery should not be wholly written off as possible motivations, a re-analysis of the sources reveals that, at times, far more pedestrian concerns played into the decision to volunteer for the yellow-fever experiments.

### The Experiments

*Phase I.* In the first days of the experiments, between August 6 and 16, 1900, Jesse Lazear, a young Johns Hopkins doctor and experimental board member, inoculated five soldiers with infected mosquitoes. The experimental protocol, including the process for selecting subjects, was haphazard at best. Reed, the lead investigator, had left Cuba and was not directly supervising the experiments. Nor did the board take seriously the mosquito theory, which had been widely dismissed in the medical press.

On August 16, 1900, Lazear inoculated himself. In an effort to confront anticipated ethical criticisms about using human subjects, the board members decided that they themselves would volunteer. The perceived level of danger that this presented, however, depended on how seriously the volunteers took the mosquito-vector theory. Throughout August 1900, the lack of confirmatory results made the mosquito-vector theory less and less plausible. After several failed inoculations with other volunteers, James Carroll (another physician board member) volunteered for self-experimentation on August 27. Several sources revealed that Carroll did not expect to get yellow fever from the inoculation because inoculations at this point were more likely to disprove rather than support the mosquito theory. It is probable the board wanted to move on to something more productive.

Everything changed when Carroll unexpectedly came down with a severe case of yellow fever a few days later. On the same day that his illness was confirmed, Lazear inoculated a Private Dean with an infected mosquito. By most accounts the inoculation was hasty and may well have been performed with a misleading disclosure of the risks to the young soldier. Dean came down with yellow fever around September 6, 1900. The spate of confirmatory results led the remaining board members to halt their own self-experimentation. Despite this, Lazear very likely inoculated himself again on September 13, with an infected mosquito. Tragically, he developed yellow fever and died 1 week later.

Why did Lazear knowingly infect himself this second time despite two confirmatory cases and the board's decision to curtail self-experimentation? One theory posits that his self-inoculation derived from guilt and sympathy for his colleague and fellow board member Carroll, who had not expected to contract the disease and had almost died from it. A better explanation is that Reed's absence, the pressure of scientific competition, and the lack of any guidelines or protocol during this disorganized experimental phase produced the circumstances that resulted in Lazear's death. This was the tragic end of the first phase [1].

*Phase II.* The second phase of the experiments began November 1, 1900. Following Lazear's death, Reed returned hastily to Cuba to design a new study protocol and supervise the experiments. The new protocol clarified guidelines for the selection and role of volunteers. While direct inoculations using infected mosquitoes continued, the second phase included several new treatment arms, such as an experimental building filled with the bodily fluids and infected clothing of those known to have yellow fever—so-called “fomites.” In this stage, volunteers were also directly injected with the blood of people known to have yellow fever.

The volunteers were now paid \$200 to participate and \$500 if they contracted yellow fever. This substantial payment, made in gold, would approximate \$8,000 and \$20,000, respectively, in today's dollars. Recent Spanish immigrants to Cuba were also sought as volunteers and were likewise well-compensated.

There is evidence that, after the public death of Lazear and confirmatory cases of Dean and Carroll, the mosquito theory became well accepted among volunteers during the second phase. For example, different arms of the experiment were regarded differently by some volunteers. And at times, volunteers refused to be moved from one protocol of the experiments to a potentially more dangerous or less desirable one [2].

*Phase III.* By August 1901, the experiments entered a third phase and were transferred from the base to a hospital in Havana. The protocol was well structured now and involved more blood-injection experiments and investigation into a yellow-fever antiserum. The mosquito theory had been presented to the worldwide medical community by Reed, based on the success of the second phase. Four out of approximately 10 volunteers in this third phase were Americans (the others were Spanish). There were three fatalities among this cohort, including the experiment's only female volunteer, an American nurse named Clara Maas.

In an interview, one American volunteer, John Bullard, made forthright comments about his motivations for volunteering. Bullard, a civilian, was attempting to start a farm in Cuba. Since volunteers received free expert medical care and were immune to further attacks of yellow fever, he concluded the following:

Volunteering to Dr. Carroll for experimental yellow fever was, I can assure you, a cold-blooded business proposition. There were no heroics in it as far as I was concerned....I suspected that I would probably get it spontaneously anyhow, so I decided I'd rather have it under favorable circumstances [3].

### **Conclusion**

Several important findings from the various phases of the yellow-fever experiments relate to volunteers' motivation to participate and their assessments of the risks. First, the experiments were conducted in different phases, and, as they evolved, so too did assessment of the potential risks. Second, there was a broad spectrum of motivations for participation. I do not wish to degrade the influence of honor and bravery which have been so wrapped up with the historical memory of these experiments. But, while honor and bravery could have been motivations, ignorance, self-interest, and simple pragmatism might also have been. In the first phase, once Reed left Cuba, the supervising board members did not take the mosquito theory very seriously and were left in Reed's absence to improvise the experimental protocol. The board members were eager for results, and pursued aggressive self-experimentation more as a means to put the mosquito theory to rest than to vindicate it.

While Lazear's bravery and martyrdom have been duly acknowledged, he most likely infected Dean, who had minimal understanding of the risks, acting against better judgment and an agreement among the board members not to do so. The rush, along with Reed's partial absence in the early phase of the experiments, no doubt led to the shoddy scientific conduct of the experiments and a division among the group

as to how seriously to view the mosquito theory. It is in this context that the initial period of human self-experimentation must be considered.

Reed was angry with his colleagues for the conduct of the first phase of the experiments. His major contribution was in the second phase, during which he designed the ingenious set of rigorously controlled experiments that satisfied international scientific criteria. But the diversity of volunteers was notable. Both Americans and Spaniards may well have been motivated by monetary inducement and fears that they were likely to get yellow fever regardless. Moreover, the presence of different experimental arms, such as the fomite volunteers, confounds the issue of motivation for bravery's sake.

Bullard's case reminds us that medical treatment was also an important motivator for participants. In a time when disease could easily strike down a young man's ambitions, it made sense to get yellow fever "out of the way," while receiving the very best medical care the U.S. Army could provide.

Heroism in the experiments, then, was not a monolithic motivation. Volunteers for the experiments represented a broad range of interests for participation, including self-interest. This is true even today, as inducements for the participation in clinical trials include monetary payments, free check-ups, psychosocial support, or receiving a potentially life-saving drug.

On the other side, just as researchers today risk their reputations on the outcomes of breakthrough studies, scientific and professional fame were very likely attractive motivators in the yellow-fever experiments. We cannot forget that yellow fever was one of the most feared diseases of its time and that its cure was a hotly pursued scientific prize.

Thus, in addition to revising the myths about honor and bravery as the sole inducements of volunteers for the yellow-fever experiments, I would like to offer the model of clinical investigation where the interests of volunteers exist in a dynamic linkage to the interests of investigators. Indeed, as Susan E. Lederer has shown, participation in an experiment can resemble the exercise of politics, where participants can resist and negotiate the terms set upon them [4]. Medical ethicists are becoming more cognizant of the political dimension—as exemplified by a vast literature and growing guidelines about the recruitment of patients into experiments, significance of payments and monetary inducements, and requirements for providing and accepting informed consent [5].

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