human volunteers in an attempt to prove that mosquitoes were responsible for the disease. Yellow fever is actually caused by a virus (yellow fever virus) with a small genome encoding ten proteins (6,7). The mosquito is the vector, that is, the transmitting agent.

The prevailing notion, before 1900, was that yellow fever is caused by bacteria. For example, Giuseppe Sanarelli of the Pasteur Institute in Paris argued that *Bacillus icteroides* was responsible for yellow fever. But George M. Sternberg, later Surgeon General of the United States, doubted Sanarelli's experiment, writing, "I would say it appears to me at the present time that…the bacillus of Sanarelli is…present occasionally and accidentally in the blood and tissue of yellow-fever patients, and that its etiological relation to this disease has not been established" (8).

In 1900, Sternberg asked Walter Reed of the US Army to assemble the *Yellow Fever Commission* to look into the large number of American troops that died in Cuba during the Spanish-American War (9,10). Over 2,000 American soldiers had died of yellow fever compared to the 400 killed in combat. Sternberg had criticized Finlay's experiments on the basis that during the inoculation stage, volunteer subjects were not isolated from the general population, and so one could not completely exclude direct transmission between humans.

Walter Reed arrived in Cuba in June 1900 with three other researchers, Jesse Lazear, Aristides Agramonte, and James Carroll. Reed's tests for the bacteria proved negative. Reed's group established that the vector was filterable through a Berkefeld filter, excluding a bacterial agent (11). A number of problems prevented Walter Reed's experiments with mosquitoes from working right away. First, Reed did not know that, for a mosquito to transmit yellow fever, the virus needed to be sitting in the mosquito's body for 12 days (incubation period). Also, he did not know that during cold weather, this incubation period needed to be adjusted. Reed conducted a negative control experiment, where human volunteers wore clothing and bed sheets stained by sweat, vomit, and feces, from yellow fever patients. The goal of this experiment was to prove that contact with fluids from disease victims could not cause yellow fever, and that what was required was exposure to the mosquito. This type of control is exactly like that used by Joseph Goldberger, when he proved that pellagra is not an infectious disease (12).

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