Epidemiol. Infect. (2005), **133** (Suppl. 1), S7–S8. © 2005 Cambridge University Press
doi:10.1017/S0950268805004218

1. Walter Reed and yellow fever

Reed W. J Hyg 1902; **2**: 101–119

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The background

For over two centuries yellow fever (YF) had terrorized those visiting and living close to endemic areas. Prompted by continued imports and its impact on US troops in the Spanish–American War of 1898, US Surgeon-General George Sternberg sent a small Commission to investigate the problem in US-occupied Cuba. It comprised James Carrol, Jesse Lazear and Aristide Agramonte; its leader was Surgeon-Major Walter Reed. Whilst in Cuba they collaborated with Cuban Juan Guitéras of Havana's Sanitary Department and Surgeon-Major William Gorgas, American chief of the island's Sanitary Department.

They arrived in June 1900, and soon published important but preliminary information in relatively obscure American journals. Then, in April 1902, Reed published a review incorporating additional data in the second volume of this journal [1]. This was an important scoop for the new journal, no doubt secured by Nuttal's contact with Reed via time spent at Johns Hopkins University. Reed's intention was that 'English and Colonial readers may … form an intelligent opinion concerning the permanent value of this work.' In fact the results obtained were of considerable permanent value. Reed died in 1902 [2], so, although the Commission's papers were later reprinted [3], Reed himself could not add anything to his journal account.

The Commission's work

Aetiology

The cause of YF was unknown; many favoured Sanarelli's claim for '*Bacillus icteroides*' which Reed and Carroll doubted. However, if a bacterial cause was found it would immediately help studies on the diagnosis, transmission and control of YF, and perhaps provide a vaccine. However, no evidence of a causal bacterium was found by culture of material which produced YF by inoculation of volunteers; nor could any be detected by histology of autopsy material.

It was already known that some diseases (tobacco mosaic, foot-and-mouth disease, myxomatosis) could be transmitted by bacteria-free filtrates – the beginnings of ideas about the 'filterable ultra-microscopic organisms' we now know as viruses [4]. Reed knew of Loeffler and Frosch's work on foot-and-mouth disease [5], and showed that serum from YF patients caused disease in inoculated volunteers after it had been passed through Berkefeld filters [Reed's Table 1].

They concluded: 'yellow fever, like the foot and mouth disease of cattle, is caused by a microorganism so minute in size that it might be described as ultra-microscopic'. This was the first such observation on a human disease [4].

Transmission ('*propagation*')

Despite considerable improvements in sanitary conditions YF remained a problem in Cuba. It was known to be infectious, but its ability apparently to jump long distances suggested that close contact and fomites were not essential. Carlos Finlay had suggested in 1881 that mosquitoes were involved but this had not been confirmed. Reed, who knew of Ross's work on malaria, discussed the problem with Finlay [6], and possibly with visitors from Liverpool [7]. Consequently, Reed set out to investigate the possible roles of fomites and mosquitoes.

Non-immune volunteers held in mosquito-proof accommodation wore clothes and slept on bedding heavily soiled by YF patients, but remained well.

Mosquitoes (*Aedes aegypti*, then called *Stegomyia fasciata*) obtained from Finlay's breeding stock were fed on YF patients and then on volunteers. Initially YF was transmitted in this way in 2/11 individuals, one of whom was Carroll. In a definitive trial from December 1900 to February 1901 transmission was successful in 14/16 cases; 10/12 are shown in Reed's Table 2. All the volunteers recovered. The earlier failures were probably due to the finding that mosquitoes had to bite a patient early in the disease, but only became infectious after about 12 days. These results were confirmed very quickly by Guitéras [8], whose results Reed summarized in Table 3.

Control

With information on transmission available, steps could be taken to break the chain of infection. As summarized by Reed, Gorgas freed Havana from YF within 90 days. The method involved using screens to prevent access of mosquitoes to YF cases, and by using pyrethrum to immobilize mosquitoes in infected houses; they were then collected and destroyed. So, at this stage control was based on preventing spread from index cases, rather than controlling the vector's habitat.

Comment

Even by today's standards, the trials were well-planned and controlled. However, everything depended on human cases to provide infective material and volunteers to detect it. Clinical diagnosis was not always certain; 25 of Guitéras's cases were excluded on this criterion.

Reed was fully aware of the 'grave sense of responsibility, at times well-nigh insupportable' of volunteer studies [5]. Carroll, intentionally infected, recovered but Lazear, accidentally bitten by a mosquito which was then allowed to feed off him, died. In addition three of Guitéras's first seven volunteers also died [8].

Such studies would now be unthinkable, but it is difficult to see how else the results could have been obtained at that time. The innumerable lives soon to be saved as a result of these studies were literally living testimony to the bravery and sacrifice of these workers and their volunteers.

Later work

The implementation of simple control measures had an immediate effect. Soon, Gorgas began to attack the vector's breeding sites by drainage, oiling, and mosquito-proofing water. He was appointed to supervise sanitary measures in Panama and his methods, also applicable to malaria, led directly to the successful completion of the Panama Canal, construction of which had been abandoned because of these diseases. However problems remained. The importance of simian YF was recognized, as were other, less-important, insect vectors [9]. Claims that YF had a bacterial aetiology persisted, but the viral cause and a simian model was established in 1927 by Adrian Stokes [10].

The price remained high. Stokes was one of five researchers to die from YF during 1927–1930 [11]. Twenty-seven others recovered, including Max Theiler who developed a mouse model and the successful 17D vaccine. Theiler received the Nobel Prize in 1951 for his work on YF. There were suggestions that Finlay, Carroll and Agramonte should also receive the Nobel Prize; this would have been unfair to Gorgas, but Reed's death would have made him ineligible.

References

1. **Reed W.** Recent researches concerning the etiology, propagation, and prevention of yellow fever, by the United States Army Commission. J Hyg 1902; **2**: 101–119.
2. **Nuttal GHF.** In memoriam: Walter Reed. J Hyg 1903; **3**: 292–296.
3. **Reed W, Carroll J, Lazear J, Agramonte A.** Yellow fever. Washington: 61st US Congress Senate Papers, 822: 1911.
4. **Waterson AP, Wilkinson L.** An introduction to the history of virology. Cambridge: Cambridge University Press, 1978.
5. **Reed W, Carroll J.** The etiology of yellow fever: a supplemental note. Am Med 1902; **3**: 301–305.
6. **Reed W.** Propagation of yellow fever: observations based on recent research. Med Rec 1902; **60**: 201–209.
7. **Durham H, Myers W.** Liverpool School of Tropical Medicine: yellow fever expedition. Some preliminary notes. Br Med J 1900; **2**: 656–657.
8. **Guitéras J.** Experimental yellow fever at the Inoculation Station of the Sanitary Department of Havana. Am Med 1901; **21**: 809–817.
9. **Strode G (ed.).** Yellow fever. New York: MacGraw-Hill, 1951.
10. **Stokes A, Bauer JH, Hudson NP.** Experimental transmission of yellow fever. Am J Trop Med 1928; **8**: 103–164.
11. **Berry GP, Kitchen SF.** Yellow fever accidentally contracted in the laboratory. Am J Trop Med 1931; **11**: 365–434.