

► **Yellow jack**

From the Panama Canal to Philadelphia, yellow fever has brought tropical death on mosquitoes' wings.

BY MARK S. LESNEY

The scene is a coastal city centuries ago, the 17th, 18th, or 19th, no matter. A yellow flag—the emblematic yellow jack—snaps in the wind on a sails-stripped schooner sitting woefully within sight of the haven of homeport. By law forbidden, no sailor may debark but must remain in quarantine with death in the hold and disease at the helm. Smallpox perhaps, typhoid fever maybe, or as likely the infamous scourge that took the emblem's name—yellow jack, yellow fever (see box, *The Flying Dutchman*).

Yellow fever is primarily a disease of the tropics. The mosquito-borne viral disease can be violent in its symptoms, and deadly. Sudden headache, fever, and muscle pain can progress to severe nausea, uncontrollable and completely debilitating hiccups, and violent vomiting—turning black as the patient enters the toxic and commonly lethal phase. Severe jaundice and bleeding from the mouth, nose, and even pores are common symptoms on the road to death. A false, some say cruel, remission phase of up to 24 hours frequently occurs in patients who subsequently relapse into symptoms and die.

Rush to judgment

Throughout history, yellow fever has been a frequent visitor to the United States. Some of its most devastating epidemics on these shores were in the 18th century. Epidemics ranged from the Deep South to Boston.

As much as for its toll on human life, the 1793 outbreak in Philadelphia was particularly notable in that it fostered internecine warfare among medical practitioners and resulted in the politicalization of treatment options, as part of a savage competition between nascent political parties in the new

nation. Famous physician Benjamin Rush, a practitioner and promoter of the newer “heroic” medicine of bleeding and mercury purges (and a favorite son of the Federalist party, which included Alexander Hamilton), became embroiled with his personal and political (Republican) enemies, who promoted an equally useless (if less harmful)



Walter Reed (upper left), Jesse Lazear (lower left), and other members of the Yellow Fever Commission.

treatment of “bark (quinine) and wine” as a cure for the fever.

Although never completely prescribed along party lines, Philadelphians came to refer to the treatments as the “Republican cure” or the “Federalist cure”. Equally politicized was the belief in the contagion's source. In general, the Federalists blamed foreign importation rather than local con-

ditions, highlighting a growing national Francophobia. By chance, significant deaths occurred among the national Republican leadership, prompting John Adams to claim that the deaths prevented a second revolution by depriving the opposing party of its two most prominent spokesmen.

By the mid-19th century, things had little changed—and the shock and surprise of a yellow fever epidemic were still met by equal parts panic and ignorance. Particularly well documented is the travail caused by the disease in Norfolk, VA, in 1855. Doctor of Divinity George D. Armstrong, who lived through the nightmare, nearly dying of the disease, told his tale of a city under siege, its citizens behaving scarce differently from the madness brought on by outbreaks of the black plague in the Middle Ages. People fled the city for outlying townships, to be met not with Southern hospitality but with regulations of expulsion after fines (for whites) or whippings (for blacks). In Norfolk itself, some victims were abandoned upon the first symptom of the disease, left to die alone. To counteract this trend, a charitable organization was instigated, according to Armstrong, “for the protection of the sick and suffering from the inhumanity of men mad through terror.”

Mosquito cost

With the great awakening to the microbial source of disease in the latter part of the 19th century through the work of Pasteur and Koch, the search for the causal organism of yellow fever reached a fever pitch. The assumption that it was caused by a bacterium (viruses were as yet unknown) led to many false leads, with various proposed bacterial species rising and falling in favor as suspects.

Because the disease did not appear to be directly transmitted from patient to patient, a mosquito vector was considered as early as 1848 and seriously proposed as a mode of transmission in 1881 by Cuban physician Carlos J. Finlay. But it was not until the needs of the military became critical during

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the Spanish-American War that the full weight of sponsored medical research was turned to the problem, and the case for an insect vector was finally proven.

The Yellow Fever Commission was established in Cuba under the leadership of Major Walter Reed, an army surgeon. Together with his colleagues, he turned his attention to possible vectors. With a cadre of human volunteers (including themselves), these doctors ultimately proved the case for mosquito transmission in 1900.

Reed was convinced of the need for human experimentation. Under his direction, Carlos Finlay's theory was tested using mosquitoes fed on infected individuals and transferred to healthy volunteers, among them Jesse Lazear, an assistant surgeon to whom the disease proved rapidly fatal. Camp Lazear, named in his honor, was established just outside Havana to complete the experiments. Two theories were tested using two separate buildings. In the "infected-mosquito building", volunteers were bitten several times and then placed in quarantine for monitoring. In the "infected-clothing building", occupants unpacked containers of soiled bed linens and clothing from yellow-fever victims in the local hospitals. Mattresses, towels, and sheets covered with black vomit and bloody discharges formed their bedding. Each morning, they retreated to quarantine.



Camp Lazear, 1898. Yellow fever buildings are indicated.

Using these methods, the commission conclusively showed that the disease was transmitted not by exposure to contaminated materials (fomites) but by the insect

bites. Blood from infected patients also proved infectious if taken soon after symptoms occurred and injected into healthy volunteers.

Victorious vaccine

The viral nature of yellow fever was first demonstrated in the 1920s, when the disease was shown to be caused by a filterable agent by A. F. Mahaffy and colleagues of the Yellow Fever Commission staff. The researchers developed a rhesus monkey model of the disease using virus-infected blood obtained from an infected West African man named Asibi. These discoveries led to the push to develop a vaccine, although it was not until the 1930s that two live attenuated virus vaccines were produced.

The first vaccine used a "French strain" of live virus isolated at the Institut Pasteur in Dakar in 1927; it is known as the French neurotrophic vaccine because it was passed from humans through the mouse brain. The second vaccine is known as the 17D vaccine from the Asibi virus, and it was passed through embryonic mouse tissue and then cultured in embryonated chicken eggs. The French strain was used until 1980. Strain 17D is currently the primary strain used for vaccine production.

The World Health Organization (WHO) promotes a continuing public health initiative aimed at the prevention and control of yellow fever. But despite the success of the vaccine and the knowledge of its host and viral etiology, yellow fever is not extinct. It remains a risk in 34 African countries, only

half of which have developed policies for childhood immunization. With the risk of global warming and the spread of viral vectors and viral strains (witness the incidence of West Nile Virus in the United States), it is sobering to remember yellow fever's infamous past.

Further reading

Armstrong, G. D. *The Summer of the Pestilence*; W. S. Dawson, Co.: Virginia Beach, 1994; <http://users.visi.net/~cwt/sum-pest.html>.

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Vainio, J.; Cutts, F. *Yellow Fever*; World Health Organization: Geneva, 1998; www.who.int/vaccines-documents/DocsPDF/www9842.pdf.

Walter Reed Collection; <http://yellowfever.lib.virginia.edu/reed/commission.html>.

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The yellow fever virus

Yellow fever is caused by a mosquito-borne single-stranded positive-RNA *Flavivirus*. The 43-nm viral particle consists of a nucleoprotein core and lipoprotein envelope. Normally endemic to the tropical regions of Africa and the Americas, the primary vector is *Aedes aegypti*. The virus is taken up when the female insect feeds on an infected animal. The mosquito remains infected for life, and the virus can be transmitted to its progeny transovarially. Nonhuman primates act as additional reservoir species.

The Flying Dutchman

Quarantined ships and death from the sea—this is the source of *The Flying Dutchman* legend. As told by Sir Walter Scott, the ship was "a vessel doomed to haunt the seas around the Cape of Good Hope because yellow fever broke out and no port would give her harborage, and all the crew perished." Throughout the history of the New World, quarantine was the oft-failed remedy for countless outbreaks of yellow fever. According to WHO, the first recorded outbreaks of the disease occurred in Guadalupe and the Yucatan in 1648. Thereafter, ships of the slave trade carried yellow fever victims and contaminated vectors from port to port, from the Americas to Africa, making yellow jack a major fear along the Atlantic trade routes. The disease also caused outbreaks at various times in history throughout Europe, from Italy to England. According to WHO, yellow fever has mercifully spared Asia.