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Yellow fever in the Americas

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This is now known: yellow fever is a vaccine-preventable hemorrhagic fever caused by a single-stranded RNA flavivirus and transmitted by mosquitoes according to two distinct epidemiologic patterns. *Aedes aegypti*, a short-winged household mosquito that breeds in standing water, transmits urban yellow fever, the classic epidemic form of the disease. Various tree-hole–breeding mosquitoes that typically spend their winged lives in forest canopies transmit jungle (or sylvatic) yellow fever to nonhuman primates and occasionally to humans, causing sporadic cases that can then re-introduce the disease into urban areas. The price paid for these essential facts included the lives of investigators and human volunteers. Lessons learned from the history of yellow fever (Box 1) include the impact of population movements, civil unrest, and poor sanitation on the spread of new pathogens; the potential for dubious ethical practices and vainglory to sully the spirit of scientific inquiry; and the ability of nature to thwart grandiose ambitions and to serve up new problems just when it was thought old ones had been solved [1,2].

Yellow fever before the twentieth century

Yellow fever is characterized clinically by fever; viremia; jaundice; and in its fulminant form by prostration, hemorrhage, shock, and variable organ damage involving mainly the liver, kidneys, and heart. Its salient features are common to a great many diseases including malignant tertian (*Plasmodium falciparum*) malaria; Weil's syndrome (*Leptospira icterohaemorrhagica*); and

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Box 1. Some events in the history of yellow fever in the Americas

1648: An epidemic of probable yellow fever erupts in the Yucatan Peninsula
1693: An English fleet with yellow fever aboard brings yellow fever to New England, where several fatal cases occur among the local population.
1699: Outbreaks in Charleston and Philadelphia presage the problem of ''yellow jack'' in North American coastal towns and cities.
1793: An epidemic in Philadelphia kills about 10% of the population and sparks debate between ''contagionists'' and ''anti-contagionists.''
1799: Noah Webster publishes *A Brief History of Epidemic and Pestilential Diseases*, making him perhaps America's first epidemiologist.
1802: Stubbins Ffirth, a Philadelphia medical student, begins self-experiments to disprove the theory of contagion.
1803: Napoleon, influenced in part by decimation of his troops by yellow fever, sells the Louisiana Territory to the United States.
1807: John Crawford of Baltimore suggests that mosquitoes might transmit various diseases.
1848: Josiah Clark Nott of Alabama postulates an insect vector for yellow fever and begins to pursue this idea.
1854: Luis Daniel Beauperthuy of Venezuela suggests a mosquito might transmit yellow fever.
1878: Yellow fever ascends the Mississippi River to St. Louis, causing an especially severe epidemic in Memphis, Tennessee.
1881: Carlos J. Finlay of Havana publishes his hypothesis that a specific mosquito (*Cubex cubensis*, now *Aedes aegypti*) might transmit yellow fever.
1880s: Yellow fever in Panama kills tens of thousands of French workers, causing Ferdinand DeLesseps to abandon his attempt to build a canal across the isthmus.
1897: Giuseppe Sanarelli, working in Brazil and Uruguay, claims that yellow fever is due to *Bacillus icteroides.*
1898: Henry Rose Carter documents an ''extrinsic incubation period'' of about two weeks between primary and secondary cases of yellow fever.

1898: Outbreak of the Spanish American war sets off a chain of events that will make yellow fever a major concern of the United States Army.
1900: Jesse W. Lazear dies of yellow fever probably acquired as a self-experiment to confirm the mosquito hypothesis. The Reed Commission makes its preliminary report.
1901: The Reed Commission publishes its definitive proof of the mosquito hypothesis based on data obtained at Camp Lazear.
1902: William Crawford Gorgas supervises the eradication of yellow fever from Havana by controlling *Aedes aegypti*.
1905: The last epidemic of urban yellow fever in the United States occurs in New Orleans.
1906: Gorgas supervises the eradication of yellow fever from Panama, enabling Americans to construct a canal across the isthmus.
1908: Oswaldo Cruz supervises the eradication of yellow fever from Rio de Janeiro.
1916: The Rockefeller Foundation begins its commitment to eradicate yellow fever.
1918: Hideyo Noguchi, working in Ecuador, claims that yellow fever is caused by a spirochete, *Leptospira icteroides.*
1925: The Rockefeller Foundation opens a laboratory in Yaba, Nigeria, to investigate the etiology of yellow fever.
1927: Adrian Stokes, Johannes Bauer, and Paul Hudson report the experimental transmission of yellow fever to rhesus monkeys, which quickly establishes the viral etiology.
1930: Theodore B. Hayne becomes the last of six investigators aliated with the Rockefeller Foundation to die of yellow fever, the others being Howard B. Cross (1921), Stokes (1927), William A. Young (1927), Noguchi (1928), and Paul A. Lewis (1929).
1930: Max Theiler demonstrates that white mice are susceptible to yellow fever by intracerebral inoculation, which leads to a ''mouse protection test'' for seroepidemiologic studies and to an eective vaccine.
1931: Wilbur A. Sawyer and colleagues begin immunization of laboratory workers against yellow fever.
1933: Fred L. Soper and colleagues report an outbreak of yellow fever in a rural area of Brazil in which *Aedes aegypti* was not present, suggesting other vectors.

(*continued on next page*)

1935: Soper and colleagues, on the basis of extensive epidemiologic studies in Brazil, become convinced of the importance of jungle yellow fever in sustaining the disease.
1937: Large-scale immunizations with the 17-D yellow fever vaccine are begun.
1938: Raymond Shannon, Loring Whitman, and Mario Franca demonstrate transmission of yellow fever with a naturally infected, wild-caught *Haemagogus spegazzinii*.
1938: Jorge Bosell shows that *Haemagogus* mosquitoes spend their winged lives in the forest canopy.
1942: Administration of yellow fever vaccine in combination with a small amount of ''normal human serum'' to American servicemen causes an estimated 28,000 cases of hepatitis with 64 deaths; contamination of the serum was subsequently traced to a single asymptomatic blood donor.
1951: Theiler receives the Nobel Prize for his work that led to the discovery of the 17D vaccine.
1985: Charles M. Rice and colleagues at the California Institute of Technology report the complete nucleotide sequence of the 17D vaccine strain of the yellow fever virus.
1989: Thomas P. Monath demonstrates that only one in two persons sustaining a primary infection with yellow fever becomes symptomatic, and that the mortality is a function not only of host susceptibility but also of the virulence of the infecting strain.
1997: Joy McFarland and colleagues report from Tennessee a case of imported yellow fever in a United States citizen (the most recent previous case of yellow fever in the United States having been in 1924).
2002: The World Health Organization estimates that yellow fever aects each year up to 200,000 persons with up to 30,000 deaths.

viral hepatitis. Recent genomic sequence analyses suggest that the yellow fever virus evolved from other mosquito-borne viruses about 3000 years ago in Africa, where it no doubt caused numerous deaths [3]. The virus was almost surely brought from Africa to the Americas by Dutch slave traders during the 1640s. An outbreak of probable yellow fever occurred in Barbados in the fall of 1647. The first epidemic generally accepted to have been yellow fever occurred in Yucatan in 1648, described in a Mayan manuscript. During that and the follow year, outbreaks occurred in St.

Kitts, Guadeloupe, and Cuba. The disease spread from one part of the Caribbean basin to another as a result of increasing ship travel, continued importation of slaves from West Africa, warfare, buccaneering, and civil unrest. Spanish-speaking peoples came to call the disease "vomito negro" after the "black vomit" from gastrointestinal hemorrhage. During the War of the League of Augsburg (1689 to 1697), a French warship brought yellow fever to Martinique, where the disease was called "mal de Siam." In 1693, an English fleet under Sir Francis Wheeler entered the Caribbean to help the colonials fight the French. Wheeler withdrew and returned to Boston, losing half of his troops along the way and introducing yellow fever to New England. In 1699, outbreaks occurred in Charleston and Philadelphia. By the turn of the eighteenth century yellow fever occurred in the West Indies, parts of what is now Latin America, and coastal cities of what is now the United States.

During the early years of the eighteenth century, yellow fever continued to frustrate English and French ambitions in Latin America and to strike seaports along the North Atlantic coast, most notably Charleston (1706, 1728, 1732, 1739, 1745, and 1748); Philadelphia (1741 and 1747); and possibly New York (1743, 1745, and 1748). The disease diminished during the years leading up to the American Revolution and then disappeared in the North Atlantic port cities until the 1790s. In 1793, outbreak of another war between England and France and a slave rebellion in what is now Haiti were followed by an epidemic which may have begun in Grenada and soon spread to St. Vincent, Barbados, Tobago, Dominica, Antigua, St. Kitts, and Trinidad. Many considered it a new disease. That same year, yellow fever struck Philadelphia with a vengeance, killing an estimated 10% of the population [4,5].

The Philadelphia epidemic of 1793 is especially notorious [6–8]. The City of Brotherly Love was hardly that. Friends and neighbors shunned one another in the streets. Families often banished their members including the frail elderly to the streets at the first signs of illness. Among those who gallantly stayed and attended the sick was Benjamin Rush who, unfortunately, concluded on the basis of scanty evidence and without statistics that bloodletting along with calomel and other "heroic" therapies was effective. William Cobbett, using data from local bills of mortality, argued to little avail that Rush was killing his patients rather than curing them [9]. Rush's publications on yellow fever augmented his already enormous reputation. As Americans increasingly turned to Philadelphia rather than to Edinburgh or Paris for their medical educations, Rush's advocacy of bleeding gained wide influence and probably contributed to the deaths of numerous citizens [10].

Philadelphians and their contemporaries pondered at length the mode of transmission. The ensuing debates, which generated at least 80 books and pamphlets in English between 1792 and 1802, are usually if perhaps simplistically framed as a contest between "contagionists" and "anticontagionists." The contagionists, observing that yellow fever in the North Atlantic port cities was identical to that in the West Indies, argued that the

epidemics never arose from within the United States. They urged vigilant quarantine of arriving ships as the basic defense. The anticontagionists, also known as "environmentalists," averred that no matter how the disease might be introduced it would take hold only if local conditions were favorable. Pointing to the filthy waterfronts and to the similarity between the symptoms of yellow fever and those of the other common bilious, remittent, and intermittent fevers of that era, the anticontagionists advocated extensive sanitary measures, such as sewer construction, waste removal, and comprehensive city planning. In retrospect, both positions had merit. Urban yellow fever is typically imported from another locality but takes hold only if breeding conditions are right for *A aegypti*. By the 1820s, most physicians and public health officials sided with the anticontagionists, whereas laypersons usually sided with the contagionists. Prominent among the laypersons siding with the anticontagionists was Noah Webster, who is best known today as a lexicographer (Webster's *Dictionary*) but whose publication in 1799 of *A Brief History of Epidemic and Pestilential Disease* makes him perhaps America's first epidemiologist [11].

Whereas prominent personages, such as Rush and Webster, pushed their anticontagionists arguments, Stubbins Ffirth, a medical student at the University of Pennsylvania from Salem, New Jersey, sought to resolve the issue by self-experimentation. Ffirth noted that secondary cases of yellow fever among persons with direct patient contact, such as physicians, nurses, family members, and gravediggers, were rare. In 1804, Ffirth reported in his graduation thesis that he had shared a bed with a patient suffering from "black vomit"; had allowed patients to breathe in his face; and had injected black vomit into his forearms, dripped it into his eyes, and swallowed it. He also injected himself with blood from yellow fever patients, who were no doubt past the viremic phase of the disease. Ffirth concluded: "As the disease cannot be communicated by the secretions or excretions, it is at least very doubtful whether it is ever communicated from one person to another, and certainly never by means of contagion." At the very least, his experiments proved the robustness of his constitution [12,13].

However right the contagionists and anticontagionists may have been, their arguments did little to control yellow fever during the early decades of the nineteenth century. Yellow fever continued to be a major problem in the Caribbean. Decimation of Napoleon's troops in Santo Domingo by various diseases including yellow fever strongly influenced his decision to sell the vast Louisiana Territory to the United States. As trade flourished and coastal towns evolved into cities along the North Atlantic coast, yellow fever affected nearly every significant port between East Brownsville, Texas, and Portsmouth, New Hampshire. By 1805 there had been frequent outbreaks in Boston, New York, Philadelphia, Norfolk, and Charleston, and also outbreaks in smaller population centers, such as Newburyport; Providence; New London; New Haven; Wilmington, Delaware; and Wilmington, North Carolina. Yellow fever seems to have been reintroduced year after year into

the major port cities, with the attacks increasing in severity until the 1850s. Death rates of 5% to 10% of the population were not uncommon. In 1853, an estimated 28% of the population of New Orleans (8000 to 9000 people) perished from yellow fever. In 1855, an estimated one third of the white population of Norfolk, Virginia, succumbed to the disease, as did more than 40% of the white population of Portsmouth, Virginia. In North America the disease was commonly known as "yellow jack," after the quarantine flag that so frequently adorned ships in harbor.

The social consequences were staggering. Confirmation of yellow fever in a port city brought commerce to its knees and caused an exodus of most of the affluent, including many physicians. As one observer put it, "For the sake of humanity, men become inhuman" [14]. The first suspected cases put physicians in a quandary. Because a positive diagnosis threatened the economy and risked the wrath of public officials and the press, physicians often hedged their bets. Disagreeing among themselves and sensing their reputations at stake, many physicians indulged in public arguments that reflected poorly on the medical profession. There were, however, examples of heroism among both physicians and laypersons. During the New Orleans epidemic of 1837, two young brothers who clerked in a local business began to visit the sick in their neighborhood, distributing medicines that had been formulated by their mother to combat yellow fever in Haiti. Their example inspired the formation of Howard Associations throughout the Southeast: groups of young men who stayed and helped the sick during yellow fever epidemics [15]. Another positive development spurred by yellow fever was the formation of health departments throughout the American South [16].

Yellow fever was relatively quiet during the Civil War, in part because of the naval blockade of Southern ports. It recurred during the 1870s, its spread promoted by the extension of railway lines and the development of steamboats. The deadliest epidemic occurred in 1878. Striking first in Baton Rouge and Vicksburg, the disease ascended the Mississippi, eventually reaching St. Louis. Hardest hit was Memphis, Tennessee. In a city of 35,000 persons, there were 15,000 yellow fever cases with 3500 deaths [14,17]. Meanwhile, the disease continued to be active in Latin America. Yellow fever, more than anything else, thwarted the French attempt to construct a canal across the Isthmus of Panama. Toward the end of the century, yellow fever subsided in the United States perhaps in part because of public health measures. The onset of the Spanish-American War in 1898, however, made yellow fever a major concern of the United States Army, which led to the elucidation of the mosquito as the vector.

The mosquito hypothesis

By the turn of the twentieth century, the debates between the contagionists and the anticontagionists were largely passé, because most physicians believed that yellow fever would eventually be shown to conform

to the germ theory. Also, mosquitoes had been shown to transmit the agents of filariasis and malaria. Why did it take so long to prove mosquito transmission of yellow fever?

The mosquito hypothesis had a long incubation. In 1807, Dr. John Crawford of Baltimore, impressed by the futility of quarantine measures, suggested that mosquitoes might be responsible for malaria, yellow fever, and other diseases. In 1848, Josiah Clark Nott, a native of Columbia, South Carolina, who was practicing in Mobile, postulated that yellow fever might be caused by an "animalcular cause" transmitted by an insect vector. Nott (Fig. 1) [18], who would later lose four of his children during a single yellow fever epidemic, also argued that mild cases occurred and might even outnumber severe cases [19]. In 1854, Luis Daniel Beauperthuy, a French-born physician practicing in Venezuela, suggested an insect vector by which he probably meant mosquitoes. The most ardent advocate of the mosquito hypothesis was Carlos Juan Finlay y Barres (or Carlos Finlay, for short) of Havana, Cuba. Possibly influenced by Manson's demonstration of a mosquito vector for filariasis, Finlay [20] posited a specific mosquito: *Culex cubensis* (later known as *Stegomyia fasciata* and now as *A aegypti*). Finlay made more than 100 attempts to transmit the disease by allowing mosquitoes to feed on patients with the disease and then on nonimmune volunteers. Two essential facts about yellow fever explain Finlay's failure to prove that mosquitoes transmitted the disease. First, patients are viremic only during the first several days of clinical illness, during which symptoms are nonspecific. Second, most mosquitoes require about 2 weeks of viral incubation before becoming infectious. Finlay probably fed most of his mosquitoes on diseased patients too late, and he invariably exposed his volunteers too early.

Yellow fever was relatively quiescent in the United States during the closing decades of the nineteenth century. In 1884 and again in 1888, bills were introduced in the United States Senate authorizing a prize of $100,000 for a breakthrough discovery, but neither bill made it out of committee hearings [21]. There was more interest in Latin America. In 1885, Domingos Freire, a Brazilian described as a "self-professed disciple of Pasteur," isolated a fungus, which he called *Cryptococcus xanthogenicus*, from the blood and excretions of yellow fever victims. Freire [22] attenuated the organism by passing it through multiple experimental animals and produced a vaccine, which he gave to 418 persons just before and during an epidemic with alleged success [23]. To investigate the validity of Friere's claims, President Grover Cleveland sent to Rio de Janeiro the sanitarian George M. Sternberg, who promptly refuted them. Less readily dismissed were the claims of Giuseppe Sanarelli, who in 1897 announced that he had determined the etiology of yellow fever to be *Bacillus icteroides*. Sanarelli [24], a European-trained bacteriologist who was director of the Institute of Experimental Hygiene at the University of Montevideo, reported that his organism caused yellow fever in human volunteers and that an antiserum

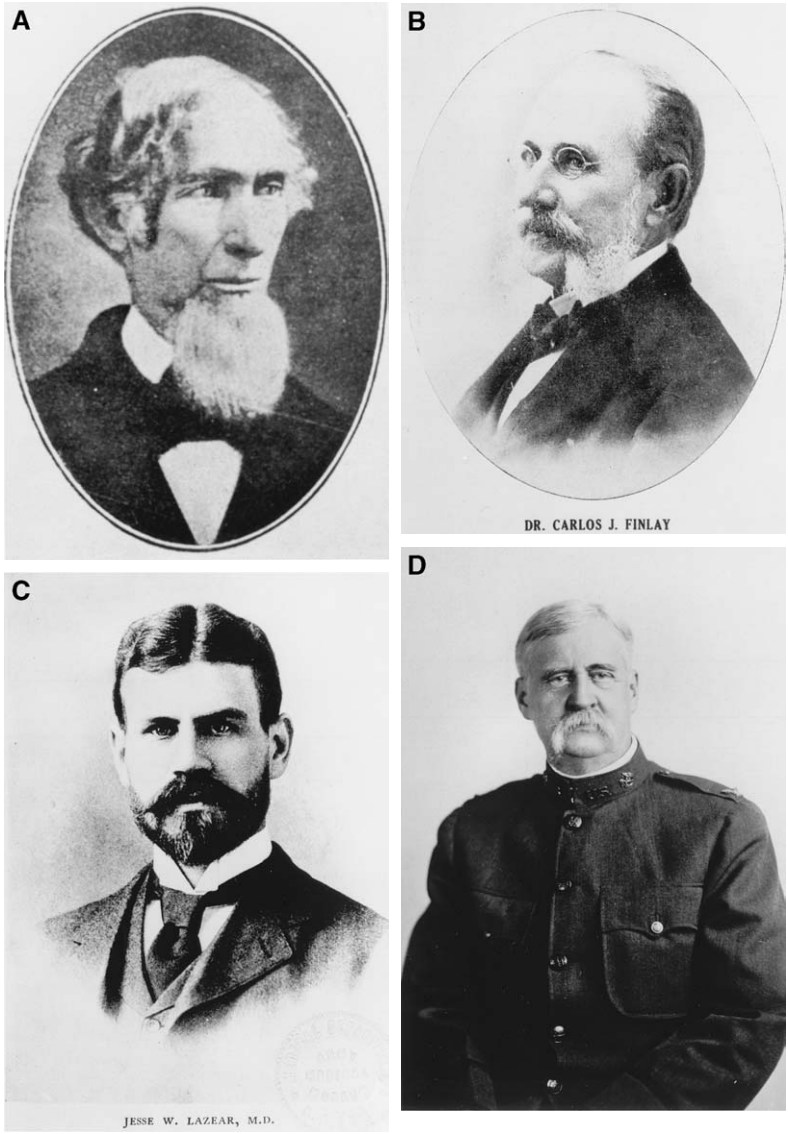

Fig. 1. Persons who contributed to the mosquito hypothesis included (*A*) Josiah Clark Nott, (*B*) Carlos Finlay, (*C*) Jesse W. Lazear, and (*D*) Henry Rose Carter. (Courtesy of the National Library of Medicine; with permission).

against it was effective therapy. Sanarelli's bacterium turned out to be the common hog cholera bacillus.

In 1898, Dr. Henry Rose Carter of the United States Public Health Service came close to supplying the key to Finlay's frustrating inability to prove the mosquito hypothesis. He studied outbreaks of yellow fever in two

northeastern Mississippi hamlets that consisted of little more than isolated plantation houses. Carter observed that 2 to 3 weeks elapsed between the first case of yellow fever in a house and additional cases in the same location. He wrote: "The fact that yellow fever is not directly transferable through an environment infected by the patient is due to the fact that the material leaving the patient must undergo some change in the environment before it is capable of infecting another man" [25]. Carter called the period required for this change the "extrinsic incubation." This observation would prove pivotal to the Reed Commission of the United States Army [26,27].

The year 1898 also marked the outbreak of hostilities between the United States and the Spanish Empire. Of the American soldiers who invaded Cuba, 13 died from yellow fever for every 1 who died in combat. Sternberg, now Surgeon General, appointed a group of four men now commonly known as "the Reed Commission" to investigate. These were Walter Reed (chairman), Aristides Agramonte, James Carroll, and Jesse W. Lazear. Fortuitously, as it turned out, Henry Rose Carter was placed in charge of the quarantine service in Havana. The Reed Commission's first order of business was to further discredit Sanarelli's *B icteroides*, a task easily accomplished. On August 1, 1900, the Board members visited Finlay in his home and listened to his views on the mosquito hypothesis. Agramonte later wrote that "the only one of us inclined to consider it favorably [was] my friend and classmate, Dr. Jesse W. Lazear." With few significant alternatives, however, the four Army surgeons resolved to test the mosquito hypothesis with nonimmune human volunteers. Finlay gave them a supply of mosquito larvae, to be kept by Lazear. Agramonte was assumed to be immune on the basis of a prior attack of yellow fever. Carroll and William H. Dean, a private in the US Army, allowed infected mosquitoes to bite them. Both came down with yellow fever and recovered. In the meantime, Reed returned to Washington. On September 8, 1900, Lazear wrote his wife: "I rather think I am on the track of the real germ, but nothing must be said as yet, not even a hint. I have not mentioned it to a soul." On September 13, 1900, Lazear apparently allowed an infected mosquito to bite him. He developed a severe case of yellow fever and died 12 days later. Hearing this news, Reed cabled that Lazear's notebook be set aside for his own use. On October 4, 1900, Reed returned to Havana and reviewed the evidence. Nineteen days later he presented a paper on the etiology of yellow fever to the American Public Health Association [28]. The paper was greeted with skepticism, one criticism being that Carroll, Dean, and Lazear might have acquired the disease from the local hospital. The next year, in a controlled environment christened Camp Lazear, Reed and his colleagues showed convincingly that *A aegypti* transmits yellow fever through a series of elegant experiments that helped established the principle of informed consent [29,30]. Reed became a celebrity and, although he died in 1902 from complications of appendicitis [31], now holds a place among medicine's immortals.

Should Reed or Lazear receive the lion's share of the credit for proving the mosquito hypothesis? This question remains unsettled barring the discovery of Lazear's notebook, which was entrusted to Reed and which has never been found. Carter had given Lazear a reprint of the paper in which he determined an "extrinsic incubation period." It seems highly likely that Lazear deduced the crucial conditions for the human experiment: the infectious agent (whatever it was) had to incubate in the mosquito for 2 weeks before the bite. Lazear wrote his wife that a stray mosquito had bitten him, and Reed reported that the bite was accidental. Apologists for Reed maintain that he did not participate in the volunteer experiments because of his age, and that he reported that Lazear's bite was accidental because the widow's pension for Mabel Houston Lazear might have been withdrawn had the death been ruled a suicide. Reviewing all of the evidence, and without denying the carefulness of Reed's confirmatory experiments, various writers assign the major credit to Lazear [32–34]. Monath [35], a current American authority on yellow fever, states unequivocally: "Lazear deserves the major credit for the experimental work proving the mosquito theory."

Hindsight tells us that the Reed Commission's reports should have ended experiments designed to transmit yellow fever to nonimmune human volunteers. They did not. By late 1901, at least four new experiments using humans were underway at Las Animas, the yellow fever hospital in Havana. Juan Guiteras, the American-trained son of exiled Cuban nationalists, returned to Cuba with the end of Spanish rule and began to test the idea that immunity to yellow fever could be produced safely by exposure to "loaded" mosquitoes. This hypothesis derived from the belief that a mild case of yellow fever in the donor patient, when transmitted through a mosquito, produces a mild case in the recipient yet results in immunity. Of his 19 volunteers, 8 acquired yellow fever and 3 died. The first two victims were young hospital employees, and the third was Clara Louise Maass (Fig. 2), a 25-year-old nurse from Newark, New Jersey, who had come to Las Animas in response to a call for nurses to attend yellow fever patients [36,37]. Guiteras [38] concluded weakly that he had confirmed the work of the Reed commission. In retrospect, Guiteras may have been working with an unusually virulent viral strain [35]. Between 1901 and 1905, a team of French investigators led by Paul-Louis Simond verified the mosquito hypothesis through experiments on 25 healthy volunteers and also demonstrated the vertical transmission of the yellow fever agent (the nature of which was still unclear) from an infected female mosquito to its eggs and larvae [39].

Proof of the mosquito hypothesis led to one of the most dramatic public health demonstrations in all of history: the eradication of yellow fever from Havana in 1902 by a team led by Colonel William Crawford Gorgas. Four years later, Gorgas accomplished the same feat in Panama enabling the construction of a canal across the isthmus [40]. In 1908, Oswaldo Cruz

Fig. 2. Persons who died during experiments conducted after proof of the mosquito hypothesis included (*A*) Clara Louise Maass, (*B*) Adrian Stokes, (*C*) Hideyo Noguchi, and (*D*) Theodore Brevard Hayne. (Photograph of Maass courtesy of the Clara Maas Medical Centers; with permission; photographs of Stokes and Noguchi courtesy of the Rockefeller Archive Center, Sleepy Hollow, New York; with permission).

supervised the eradication of yellow fever from Rio de Janeiro. There were grounds for optimism that yellow fever could eventually be eradicated by controlling the household mosquito, *A aegypti*.

The Rockefeller Foundation era: isolation of a virus, development of a vaccine, and recognition of jungle (sylvatic) yellow fever

The last epidemic of yellow fever in the United States occurred in New Orleans in 1905 [41]. By 1914, successful control campaigns were well underway in parts of Latin America including the Amazon basin. That year, Wickliffe Rose of the Rockefeller Foundation in New York City visited Malaya and the Philippines and learned that Asians feared that the imminent opening of the Panama Canal might introduce yellow fever into the Pacific basin, where it was unknown. Rose discussed this concern with Gorgas who, assuming that *A aegypti* was the only vector and that elimination of the disease in selected ''key centers'' would eliminate its reservoirs, opined that yellow fever could be ''eradicated from the face of the earth within a reasonable time and at a reasonable cost'' [42]. To that end, the Rockefeller Foundation formed a Yellow Fever Commission in 1918 with Gorgas as director. Hideyo Noguchi, a brilliant Japanese-born scientist employed at The Rockefeller Institute for Medical Research and an authority on spirochetes, went to Guayaquil, Ecuador, where he promptly isolated a spirochete from the blood of 6 of 27 patients with presumed yellow fever. Naming the organism *Leptospira icteroides*, he believed that he had found the causative pathogen. In retrospect, these patients almost surely had Weil's disease (leptospirosis), which was highly prevalent in Ecuador. Noguchi and the many authorities that accepted his finding, in part because of his enormous reputation, either ignored or discounted the observation by James Carroll of the Reed Commission and confirmed by Oswaldo Cruz in Brazil that, whatever the agent might be, it could pass through a Berkefeld filter. Yellow fever was eradicated from Ecuador in 1919, and the next year Gorgas and his colleagues beamed that ''the brilliant work of Noguchi in discovering the organism causing yellow fever already is having some effect on the control of the disease'' [43]. Optimism peaked in 1925, when only three cases of yellow fever, all in one area of northern Brazil, were reported in the Western Hemisphere.

Such optimism was tempered by reports of yellow fever, or something like it, in Africa [44,45]. In 1925, the Rockefeller Foundation organized a West African Yellow Fever Commission and charged it not only to characterize the regional epidemiology but also to isolate the causative organism. Henry Beeuwkes, a retired Army colonel, was placed in charge of the headquarters at Yaba, a suburb of Lagos, Nigeria. Unable to isolate Noguchi's spirochete from a single case, Beeuwkes gave top priority to developing an animal model. Injecting blood from infected patients into

native animals did them no harm. Reasoning that these animals might have acquired resistance through evolution, Beeuwkes imported new animals including rhesus monkeys. On June 30, 1927, A.F. Mahaffy of the Rockefeller Foundation injected blood from a 28-year-old Nigerian named Asibi into a rhesus monkey, which died 5 days later. The monkey's blood caused fatal yellow fever in a second monkey, and the process continued until "approximately thirty animals were inoculated in this way with fatal outcome in all instances except one; rhesus 353 developed fever but recovered" [46]. First authorship on this report, which rivals in importance the findings of the Reed Commission, was awarded posthumously to Adrian Stokes, a pathologist from the famous Stokes medical family of Dublin, Ireland. Stokes almost surely acquired yellow fever from performing autopsies on the infected monkeys. He asked for an autopsy should he die, that mosquitoes be allowed to feed on him, and that his blood be injected into a monkey to see whether it would cause yellow fever. It did.

Although the virus isolated from Asibi proved an enormous boon to yellow fever research, there would be more heartbreak and disappointment before its ultimate fruition: a vaccine. Noguchi went to West Africa to do his own experiments to determine whether a virus, rather than his spirochete, was the real culprit. Working in secrecy, he became acutely ill and died [47]. W.A. Young performed the autopsy, confirmed yellow fever, and then died of the disease himself. In all, six researchers affiliated with the Rockefeller Foundation, from a field force that never numbered more than 27 full-time investigators, died studying yellow fever. The last of these was Theodore B. Hayne, a 32-year-old, recently married South Carolinian who died in 1930 [48]. Hayne, who was in charge of all of the infected mosquitoes at Yaba, acquired the disease during experiments with rhesus monkeys that included a "monkey protection test" to determine whether a person had antibodies to the virus. Meanwhile, in New York, laboratory studies with the virus isolated from Asibi were yielding dividends.

In 1930, Max Theiler, a South African born scientist at the Rockefeller Institute, reported: "It has been found that if yellow fever virus is injected into the brains of white mice, a certain number become ill and die" [49]. This discovery, for which Theiler would eventually receive the Nobel Prize, had two immediate implications. First, a "mouse protection test" replaced the cumbersome and dangerous monkey protection test for seroepidemiologic studies. Surveys in South America using the new tool showed that yellow fever was much more widespread than had been thought, and that it was prevalent in large areas of the Amazon basin in which the disease had not been reported. Second, it became possible to attenuate the virus through serial passages in mice and develop a vaccine. Beginning in 1931, Rockefeller Foundation laboratory personnel were given simultaneous injections of immune human serum and a live, attenuated yellow fever virus. Later, Hugh H. Smith, working in Theiler's laboratory, observed a distinct decrease in the neurovirulence at the 176th passage level of a viral

passage lineage known as 17D [50]. Theiler and Smith were the first recipients of the 17D vaccine, derived from the virus isolated from the Nigerian patient, Asibi. In 1937, widespread immunizations began with what proved to be one of the safest and most effective vaccines yet developed.

Yellow fever might indeed have been eradicated had *A aegypti* been the only vector. Rockefeller investigators in West Africa, however, noted that mosquitoes other than *A aegypti* could transmit the virus under experimental conditions. Hayne, before his death in 1930, had studied the life habits of various mosquitoes, which included tree-hole breeders and crab-hole breeders, capable of transmitting yellow fever to rhesus monkeys in the laboratory. In 1932, Bauer [51] published a definitive paper on this phenomenon. That same year, Soper et al [52] of the Rockefeller Foundation described an outbreak in a remote area of Brazil where *A aegypti* was not present [53]. Soper [54] went on to establish the essential features of jungle (sylvatic) yellow fever. Various mosquitoes, now known collectively as *Haemagogus* species in the Americas and as *Aedes* species in Africa, transmit the disease to nonhuman primates in forests and jungles and in the moist savannahs of Africa. Breeding in tree holes in the forest canopies and reaching high densities, these mosquitoes cause accidental infections in humans especially during forestry and recreational activities. Infected persons can then reintroduce the virus into urban centers where *A aegypti* breeds in man-made containers [54]. The indefatigable and politically astute Soper continued his efforts to eliminate *A aegypti* and to promote the vaccine in Latin America. In 1950, he became director of the Pan American Sanitary Bureau, the predecessor of the Pan American Health Organization. By 1972, *A aegypti* had been eliminated from 19 countries.

Yellow fever today

Yellow fever continues to be a major public health problem, affecting up to 200,000 persons with up to 30,000 deaths each year [55–57]. More than 90% of the cases occur in Africa, especially in West Africa, primarily because of breakdowns in vaccination and mosquito control programs. Jungle (sylvatic) yellow fever is especially problematic in the Amazon region, Peru, and Bolivia [58,59]. Each year, some 9 million tourists visit countries in which yellow fever remains endemic. In 1997, after 73 years during which the disease had not been recognized in the United States, a fatal case occurred in Tennessee in an American tourist who had visited the jungles of Brazil along the Rio Negro and Amazon Rivers [60]. In 1999, a fatal case occurred in California in an American tourist who had visited the rainforests of southern Venezuela. Because it is now recognized that the vaccine can cause fatal reactions, albeit rarely, conversations with patients about the vaccine are not as straightforward as they once seemed [61,62]. On

the positive side of the ledger, the genomic sequence of the virus is known and there is reason to believe that further study of its three structural and seven nonstructural proteins will eventually lead to effective drug therapies [35,63]. As a zoonosis, yellow fever cannot be eradicated. As a continuing threat to humankind including the potential for bioterrorism, yellow fever cannot be ignored. As a lesson in how our predecessors furnish examples, both good and bad, about how we should behave in the face of frustration and uncertainty, the history of yellow fever remains instructive.

References

[1] Strode WK, editor. Yellow fever. New York: McGraw Hill; 1951.
[2] Delaporte F. The history of yellow fever: an essay on the birth of tropical medicine. Cambridge, Massachusetts: MIT Press; 1991.
[3] Zanotto PM de A, Gould EA, Gao GF, et al. Population dynamics of flaviviruses revealed by molecular phylogenies. Proc Natl Acad Sci U S A 1996;93:548–53.
[4] Blake JB. Yellow fever in eighteenth century America. Bull N Y Acad Med 1968;44: 673–86.
[5] Blake JB. Yellow fever in the continental United States during the nineteenth century. Bull N Y Acad Med 1968;44:687–701.
[6] Foster KR, Jenkins MF, Toogood AC. The Philadelphia yellow fever epidemic of 1793. Sci Am 1998;279:88–93.
[7] Estes JW, Smith BG. A melancholy scene of devastation: the public response to the 1793 Philadelphia yellow fever epidemic. Canton, MA: Science History Publications; 1997.
[8] Taylor S. Yellow fever: politics and class relations in Philadelphia, 1793–1805. Trans Stud Coll Physicians Phila 1999;21:55–8.
[9] Shryock RH. Benjamin Rush from the perspective of the twentieth century. In: Shryock WH. Medicine in America: historical essays. Baltimore: The Johns Hopkins Press; 1966. p. 233–51.
[10] Waring JI. The influence of Benjamin Rush on the practice of bleeding in South Carolina. Bull Hist Med 1961;35:230–7.
[11] Rosen G. Noah Webster—historical epidemiologist. J Hist Med Allied Sci 1965;65:97–114.
[12] Ffirth S. A treatise on malignant fever; with an attempt to prove its non-contagious nature. Philadelphia: Printed by the author by B. Graves; 1804.
[13] Anonymous, Stubbins H. Ffirth (1784–1820). JAMA 1964;189:319–20.
[14] Keating JM. History of the yellow fever epidemic of 1878, in Memphis, Tennessee. Memphis: The Howard Association; 1979.
[15] Newsom EY. Unto the least of these: The Howard Association and yellow fever. South Med J 1992;85:632–7.
[16] Humphreys M. Yellow fever and the south. New Brunswick, NJ: Rutgers University Press; 1992.
[17] Baker TH. Yellowjack: the yellow fever epidemic of 1878 in Memphis, Tennessee. Bull Hist Med 1968;42:241–64.
[18] Nott JC. Yellow fever contrasted with bilious fever: reasons for believing it is a disease sui generis—Remote cause—Probable insect or animalcular origin, &c. New Orleans Med Surg J 1848;4:563–601.
[19] Downs WG. Yellow fever and Josiah Clark Nott. Bull N Y Acad Med 1974;50:499–508.
[20] Finlay C. El mosquito hipotéticamente considerado como agente de transmission de la fiebre amarilla. An Acad Cien Med Habana 1881;18:147–69.
[21] Miles WD. Prizes for yellow fever research in the 1880's. Bull Hist Med 1969;43:176–9.

[22] Freire D. Doctrine microbienne de la fièvre jaune et ses inoculations preventives. Rio de Janeiro: Impremerie Nationale; 1885.
[23] Warner M. Hunting the yellow fever germ: the principle and practice of etiological proof in late nineteenth century America. Bull Hist Med 1985;59:361–82.
[24] Sanarelli G. A lecture on yellow fever with a description of the bacillus icteroides. BMJ 1987;2:7–11.
[25] Carter HR. Note on the interval between infecting and secondary cases of yellow fever from the records of the yellow fever at Orwood and Taylor, Miss. In 1898. New Orleans Med Surg J 1900;52:616–36.
[26] Richter ED, Henry R. Carter: an overlooked skeptical epidemiologist. N Engl J Med 1967; 277:734–8.
[27] Woodward TE. Epidemiologic classics of Carter, Maxcy, Trudeau, and Smith. J Infect Dis 1992;165:235–44.
[28] Reed W, Carroll J, Agramonte A, Lazear JW. The etiology of yellow fever: a preliminary note. Phila Med J 1900;6:790–6.
[29] Reed W, Carroll J, Agramonte A. The etiology of yellow fever. JAMA 1901;36:431–46.
[30] Bean WB. Walter Reed and the ordeal of human experiments. Bull Hist Med 1977;51: 75–92.
[31] Crosby WH, Haubrich WS. The death of Walter Reed. JAMA 1982;248:1342–5.
[32] Franklin J, Sutherland J. The forgotten hero of yellow fever. In: Franklin J, Sutherland J. Guinea pig doctors: the drama of medical research through self-experimentation. New York: William Morrow and Company; 1984. p. 183–226.
[33] del Regato JA. Jesse William Lazear: the successful experimental transmission of yellow fever by the mosquito. Med Herit 1986;2:443–52.
[34] Altman LK. The myth of Walter Reed. In: Altman LK. Who goes first? The story of self-experimentation in medicine. Berkeley: University of California Press; 1998. p. 129–57.
[35] Monath TP. Milestones in the conquest of yellow fever. In: Koprowski H, Oldstone MBA, editors. Microbe hunters: then and now. Bloomington, IL: Medi-Ed Press; 1996. p. 95–111.
[36] Cunningham JT. Clara Maass: a nurse, a hospital, a spirit. Belleville, NJ: Rae Publishing; 1968.
[37] Tiggert HB, Tiggert WD. Clara Louise Maass: a nurse volunteer for yellow fever inoculations, 1901. Mil Med 1983;148:787–800.
[38] Guiteras J. Experimental yellow fever at the inoculation station of the sanitary department of Havana with a view to producing immunization. Am Med 1901;2:809–17.
[39] Tran D, Chastel C, Cenac A. Paul-Louis Simond et la mission Marchoux au Brésil. Bull Soc Pathol Exot 1999;92(5 pt 2):388–91.
[40] Litsios S. William Crawford Gorgas (1854–1920). Perspect Biol Med 2001;44:368–78.
[41] Carrigan JA. Yellow fever in New Orleans, 1905: the last epidemic. Bull Tulane Univ Medical Faculty 1967;26:19–28.
[42] Fosdick RB. The story of the Rockefeller Foundation. New York: Harper & Brothers Publishers; 1952.
[43] Gorgas WC, Carter HR, Lyster TC. Yellow fever: its distribution and control in 1920. South Med J 1920;13:873–80.
[44] Hewer TF. The discovery of yellow fever in Central Africa. J R Coll Phys London 1987;21: 199–201.
[45] Porterfield JS. Yellow fever in west Africa: a retrospective glance. BMJ 1989;299:1555–7.
[46] Stokes A, Bauer JH, Hudson NP. Experimental transmission of yellow fever to laboratory animals. Am J Trop Med 1928;8:103–64.
[47] Koide SS. Hideyo Noguchi's last stand: the yellow fever commission in Accra, West Africa (1927–8). J Med Biogr 2000;8:97–101.
[48] Bryan CS. A most satisfactory man: the story of Theodore Brevard Hayne, last martyr of yellow fever. Charleston, SC: Waring Library Society; 1996.
[49] Theiler M. Susceptibility of white mice to the virus of yellow fever. Science 1930;71:367.

[50] Theiler M, Smith HH. Effect of prolonged cultivation in vitro upon pathogenesis of yellow fever virus. J Exp Med 1937;65:767–86.
[51] Bauer JH. Transmission of yellow fever by mosquitoes other than *Aedes aegypti*. Am J Trop Med 1928;8:261–82.
[52] Soper FL, Penna H, Cardosa E, et al. Yellow fever without *Aedes aegypti*: study of a rural epidemic in the Valle do Chanaan, Espirito Santo, Brasil, 1932. Am J Hyg 1933;18:555–87.
[53] Löwy I. Epidemiology, immunology, and yellow fever: the Rockefeller Foundation in Brazil, 1923–1939. J Med Virol 1997;30:397–417.
[54] Soper FL. Jungle yellow fever: a new epidemiological entity in South America. Rev Hyg Saude Pub 1936;10:1–9.
[55] Monath TP. Yellow fever: an update. Lancet Infect Dis 2001;1:11–20.
[56] Tomori O. Yellow fever in Africa: public health impact and prospects for control in the 21st century. Biomedica 2002;22:178–210.
[57] Tesh RB. Viral hemorrhagic fevers of South America. Biomedica 2002;22:287–95.
[58] Mondet B. Considérations sur l'épidémiologie de la fièvre jaune au Brésil. Bull Soc Pathol Exot 2001;94:260–7.
[59] Vasconcelos PFC, Costa ZG, Travassos da Rosa ES, et al. Epidemic of jungle yellow fever in Brazil, 2000: implications for climatic alterations in disease spread. J Med Virol 2001; 598–604.
[60] McFarland JM, Baddour LM, Nelson JE, et al. Imported yellow fever in a United States citizen. Clin Infect Dis 1997;25:1143–7.
[61] Cetron MS, Marfin AA, Julian KG, et al. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2000. MMWR Morb Mortal Wkly Rep 2002;51(RR-17):1–11.
[62] Monath TP, Cetron MS. Prevention of yellow fever in persons traveling to the tropics. Clin Infect Dis 2002;34:1369–78.
[63] Rice CM, Lenches EM, Eddy SR, et al. Nucleotide sequence of yellow fever virus: implications for flavivirus gene expression and evolution. Science 1985;229:726–33.