ARTS & HUMANITIES

The Yellow Fever Vaccine: A History

J. Gordon Frierson

Clinical Professor Emeritus, University of California San Francisco, San Francisco, California

After failed attempts at producing bacteria-based vaccines, the discovery of a viral agent causing yellow fever and its isolation in monkeys opened new avenues of research. Subsequent advances were the attenuation of the virus in mice and later in tissue culture; the creation of the seed lot system to avoid spontaneous mutations; the ability to produce the vaccine on a large scale in eggs; and the removal of dangerous contaminants. An important person in the story is Max Theiler, who was Professor of Epidemiology and Public Health at Yale from 1964-67, and whose work on virus attenuation created the modern vaccine and earned him the Nobel Prize.

At the close of the 19th century, yellow fever was a known and feared pestilence of the western hemisphere and the coastal regions of West Africa, for which no cause or effective treatment was known. Known often as "yellow jack" because of the yellow quarantine flag on ships, the disease terrorized populations and severely disrupted trade. Though the medical profession was still in the dark on many aspects of the illness, accumulated observations had rendered certain facts clear: It occurred in epidemic and endemic form; it was associated with ports, and new outbreaks were often associated with the arrival of a ship from a known focus; a transmittable "germ" was presumed, but transmission was not direct; and recovery from the disease conferred durable immunity [1]. Patrick Manson, in his tropical medicine text of 1898, referred only to a "germ or virus," though noting that it probably required an interval of time outside the body to render it infectious [2].

The close of the 19th century also witnessed dramatic discoveries in the new science of bacteriology that would transform medicine forever. Several investigators claimed to have found bacteria responsible for yellow fever, and the first "vaccines" were created from these candidates. Because of alleged successes, Dr. George Sternberg, an army doctor often called the "father of American bacteriology," was appointed by President Grover Cleveland to investigate. His thorough study found the vaccines poorly conceived or ineffective [1], so that by the turn of the century there was essentially no progress in yellow fever prevention.

To whom all correspondence should be addressed: J. Gordon Frierson, MD, 140 Melville Avenue, Palo Alto, CA 94302. E-mail: jgfr@earthlink.net.

†Abbreviations: IHD, International Health Division.

Keywords: yellow fever, vaccine, history, cell culture, Theiler

FIRST VACCINE ATTEMPTS

After the Spanish-American War, yellow fever in the notoriously endemic Cuba became a particularly American concern. Sanitation measures in Havana (i.e., eliminating the "miasmas" with sewage disposal, clean water, and overall cleanliness) failed to curb the rising incidence. Consequently, Sternberg, as U.S. surgeon general, appointed a Yellow Fever Commission, headed by Walter Reed, to investigate. This famous commission, through careful experiments, established that mosquitoes transmitted the disease and the agent was filterable through a Berkefeld filter, excluding a bacterial agent [3,4]. Bacteria-based vaccines quickly became extinct. Many attempts to infect laboratory animals failed, however, leaving the scientific community without a laboratory model. An attempt to bypass this difficulty was made in 1901, when Dr. John Guiteras, based in Havana, noted the low mortality in the Walter Reed experiments (14 inoculations and no deaths) and attempted to immunize subjects with a tiny dose (one to four mosquito bites each) of live agent. Unfortunately eight out of 42 volunteers became ill, and three died [5]. Further work on immunization came to a halt, and most attention henceforth focused on prevention through mosquito control.

When the Panama Canal opened in 1912, large "unseasoned" populations around the world were suddenly liable to exposure. The Rockefeller Foundation's International Health Commission resolved to assist in yellow fever eradication, and in 1918, a team was dispatched to Guayaquil, Ecuador, a residual endemic center, to implement control measures. The team included Hideyo Noguchi. Noguchi, born in Japan, had risen from extreme poverty to earn a medical degree and eventually a position at the Rockefeller Institute. He already had distinguished himself by the discovery of spirochetes in brain tissue of paretics. Noguchi was aware of another spirochete, *Leptospira icterohemorrhagiae*, as the cause of Weil's disease. There was speculation that Weil's disease and yellow fever might be identical

or closely related diseases, and Noguchi sought spirochetes in Ecuador. He found some in the livers of "yellow fever" patients and was able to pass them easily to guinea pigs. He felt he had discovered the causative agent of yellow fever and strongly implied this in several publications [6,7,8]. He named the new spirochete *Leptospira icteroides* and claimed to be able to distinguish it serologically from *L. icterohemorrhagicae* [9]. In short order, he produced a vaccine and antiserum against yellow fever, both manufactured at the Rockefeller Institute, and used quite extensively in the United States, Latin America, and French African colonies [10]. The vaccine also was available in New York City for travelers (the first travel medicine clinic?) [11]. Noguchi published "successful" results on 7,964 vaccinations [12,13]. But seasoned investigators could not duplicate his results, and doubts grew [14]. The sloppy statistics of the vaccine trials, the established easy filterability of the causative agent, and the inability of others to infect laboratory animals were facts that Noguchi could not explain away [15].

Then, in 1926, Max Theiler, born in South Africa and son of a veterinarian, and Andrew Watson Sellards showed that the *L. icteroides* obtained from Noguchi was serologically identical with *L. icterhemorrhagica* [16]. In that same year, the Rockefeller Foundation quietly discontinued its distribution of the vaccine, and there was no alternate candidate.

AFRICA ACTIVITIES, ISOLATION OF VIRUS, AND A NEW HOST

After World War I, the Rockefeller Foundation expanded its yellow fever activities to Africa. The second West African Yellow Fever Commission was formed in 1925 (a prior commission in 1920 had accomplished little). The tense and tragic story of this expedition has been told many times [17,18,19,20], and only brief comments will be made here. The expedition, based near Lagos, was to determine whether African yellow fever was the same as yellow fever in South America, to find the causative agent

(including further search for *Leptospira*), and to study its epidemiology. Major Henry Beeuwkes, a Hopkins-trained bacteriologist retired from the army, led the expedition. He was joined by Adrian Stokes, a London-based professor of pathology who was an expert on leptospirosis, and others.

In June 1927, blood from a 28-year-old African named Asibi suffering from a relatively mild febrile illness, which he survived, was injected into a *Macacus rhesus* imported from India (African monkeys did not become ill). The monkey proved susceptible, establishing the infection for the first time in a suitable laboratory host [21]. Tragically, after only a brief interval to savor this discovery, Stokes perished from yellow fever, the first victim of the expedition. Noguchi arrived in November to aid in the research, trying again to verify his *leptospira* theory, which Stokes already had investigated with negative results. His laboratory was described as being in a state of confusion and his technique haphazard. He was careless about labeling and screening, secretive in his behavior, and a source of tension to a group already stressed by the primitive conditions and the mortal danger of the work. He infected an astounding 1,200 monkeys, but found no *leptospira*. With the inevitability of a Greek tragedy, Noguchi, doggedly pursuing his mistaken idea, eventually contracted yellow fever, perishing in May 1928. A third investigator, William Young, who had performed Noguchi's autopsy, also succumbed to yellow fever. The expedition was a costly one.

However, the virus now could be removed to the laboratory and properly studied. In short order, it was shown that serum from immune humans protected monkeys against infection, immune serum from South America protected against the African virus (thus suggesting that one vaccine would offer protection globally) [22], and killed virus would not confer immunity.

At the same time that the West African Commission was active, Sellards, from the department of tropical medicine at Harvard, was on his way to Dakar, Senegal, to study a yellow fever outbreak when he heard of the success establishing the virus in rhesus mon-

keys. He joined up with Constant Mathis, director of the local Pasteur Institute, and Jean Laigret, who was in charge of the "defense sanitaire" established in Dakar to cope with the outbreak. One day, Laigret noticed that the son of a woman with yellow fever did not appear for his daily visit at the hospital. He visited the house of this man, Francois Mayali, and found him with a fever. A sample of Mayali's blood produced severe yellow fever in a rhesus monkey, though Mayali suffered only a relatively mild case [23,24]. (He lived to age 62, when he died of a bronchogenic carcinoma [25].) This virus became known as the "French strain" (the other remained the "Asibi" strain). The Sellards team discovered that the virus survived freezing, allowing transport of infected liver tissue (instead of monkeys) for further passage [26].

Initially, some crude vaccines using formalin and phenol-preserved liver tissue were made, with uncertain results [27]. Clearly, a form of attenuated live vaccine, as well as a more affordable laboratory host, were needed. Theiler found a better host.

Theiler was aware that herpes simplex virus recently had been grown in mouse brain by Howard Andervont [28], and he knew about Pasteur's method of attenuating rabies virus in non-host nervous tissue. With this knowledge, Theiler inoculated mice intracerebrally and found that the virus grew well. More important, with multiple passages, while there was an increase in neurotropism, there was diminished hepatic damage and systemic illness ("viscerotropism") when given back to rhesus monkeys [29]. The first attenuated strain had been created, albeit one with increased neurotropism. Incidentally, at about the 30th mouse passage, Theiler contracted yellow fever. Fortunately for posterity, it was a light case.

COMPETING VACCINES

Meanwhile, in New York, the International Health Division (IHD†) of the Rockefeller Institute was seeking laboratory facilities to continue its yellow fever work. Simon Flexner, director of the Institute, remembering that three Rockefeller re-

searchers already had perished from yellow fever, hesitantly granted limited space provided that strict isolation policies were followed [30]. Wilbur Sawyer was appointed to head the new laboratory, and Theiler, after publishing his work on mouse brain adaptation, left Harvard to join the team.

To emphasize the hazardous nature of yellow fever work, the IHD in 1931 reported on 32 cases acquired in eight laboratories with five deaths [31]. The need for a vaccine to protect laboratory and field workers was urgent, and in the same year, the attenuated but neurotropic French strain, passaged more than 100 times in mouse brain, was given a trial. Because of concern over inducing an encephalitis, the virus was combined with immune human serum obtained from recovered laboratory staff [32,33]. The first test subject for this vaccine/serum combination was Dr. Bruce Wilson of the IHD, on leave from Brazil and as yet not immune to the disease. He was hospitalized under strict isolation, but there was no reaction beyond some redness and swelling at the injection site [30,34]. Others were then successfully vaccinated, and sera obtained after vaccination protected mice against infection. This "mouse protection test," devised by Theiler, was used with variations as a measure of immunity until after World War II [35]. The mouse brain-derived vaccine, given with immune serum, became the standard vaccine used by the Rockefeller Foundation for some time.

Meanwhile, across the ocean, Laigret had been transferred to the Pasteur Institute in Tunis, then under the direction of Charles Nicolle, winner of the 1928 Nobel Prize for his discovery of the louse transmission of epidemic typhus. Sellards and Laigret were anxious to try the mouse brain vaccine there. Nicolle was hesitant, concerned about introducing a new virus to Tunis, but agreed to trials if conducted in winter when mosquitoes were rare [36]. The two investigators prepared a vaccine from mouse brain cultures of the French strain just as Theiler had done, but without human serum. Because systemic and neurologic reactions were sometimes severe, an attempt was made to "attenuate" the virus. Initially, a three-dose regimen was tried, using

virus dried for varying periods of time, with both systemic and neurologic reactions being noted [23,37,38]. The next technique was to coat the virus particles with oil or egg yolk and freeze-dry the mixture, creating a fine powder of coated virus particles (allegedly allowing a slow release of virus) that could be reconstituted in saline on site and given as a single dose [39]. Finally, the team showed that giving this latter vaccine by scarification produced an immunity equivalent to injection, leading to the use of a combined smallpox-yellow fever vaccine [40]. The British had opted for the Rockefeller approach, vaccine combined with immune serum.

This state of affairs — the Rockefeller Foundation vaccine being used in the Western Hemisphere and England and the Pasteur Institute one-dose vaccine (usually combined with smallpox) being used in France and its African colonies — persisted for some years. The Rockefeller vaccine appeared safer, but large amounts of serum were needed, limiting its use on a large scale (attempts to use animal serum resulted in cases of anaphylaxis and were abandoned). The French vaccine risked febrile and CNS reactions but could be used in large campaigns. Using scarification, one could vaccinate up to 800 people per hour, or about 5,000 per day. By the end of 1945, about 16 million Africans had been vaccinated, in spite of the disruptions of the war [41], and 56 million by 1953 [42]. A policy of vaccinating entire populations at four-year intervals was adopted. In contrast to earlier experience, neurologic side effects were stated to be rare [43], possibly because of further virus attenuation (the number of passages had almost doubled [44]). Alternatively, surveillance for delayed reactions may not have been complete, and detailed follow-up statistics are not available.

BREAKTHROUGHS AND COMPLICATIONS

In New York, the fear of neurologic reactions to the vaccine was still a major concern. Tissue culture techniques, born at the Rockefeller Institute in the 1920s, might offer a way out. In 1932, Theiler and Eugen

Haagen succeeded in cultivating yellow fever virus in both mouse and chicken embryo tissue. But extensive passages of both the Asibi and the French strains failed to affect their neurotropic tendency, so a strategy of dissecting out the nervous tissue from the chick embryos was adopted. Eventually, at the 100th subculture of the Asibi strain in nervous tissue-deprived embryo (176th in chick embryo altogether), Hugh Smith, working with Theiler, noted that the virus failed to kill mice when injected intracerebrally — the "acid test." Attempts to repeat the phenomenon with unpassaged virus failed, suggesting that the attenuation was due to chance mutations, and more than 100 subcultures of the French strain under the same conditions showed no loss of neurotropism [45]. Animal testing showed the attenuated mutant to be safe and immunizing [46]. This breakthrough, because of a chance mutation, resulted in a strain that appeared to be sufficiently attenuated to use without protective immune serum [47]. It was given the name 17D.

At this point, field testing and preparations for large scale manufacturing of vaccine were in order. In 1937, Hugh Smith began the project in Brazil (a 13-day sea voyage at that time). By this time, the jungle cycle of yellow fever had been recognized and the goals of vaccination altered to containing the disease rather than eliminating it. The newly invented techniques of culturing virus in embryonated eggs and freeze drying were now available and utilized. Within one year, 59,000 people were vaccinated with the 17D strain without severe complications. By June 1939, the number was up to 1.3 million people, without further problems. Smith moved on to Colombia, where he initiated another successful program [48]. The way seemed clear.

However, new and instructive problems arose. In July 1941, 119 cases of encephalitis were noted in Brazil, all recipients of one lot of vaccine separated from the parent strain by only a small number of subcultures. The conclusion was that there had been an unfavorable mutation during these subcultures, and thus was born the "seed lot" system, whereby

"master seeds" are created from parent strains and kept frozen for future use, consequently eliminating extra subcultures [49].

Simultaneously, another complication was emerging. Starting in 1937, cases of delayed jaundice, sometimes clustered, were noted in England and Brazil [50,51]. Serum was suspected as the source [52]. Because the virus was unstable in water and saline, a small amount of human serum had been used as a protein source to provide stabilization during filtration. The use of serum was abandoned in Brazil, aided by sterile techniques to avoid filtration, and no further cases occurred. But this complication would appear again elsewhere.

The outbreak of World War II created new and huge demands for vaccine. An epidemic of yellow fever near the North African War zones early in the conflict made clear the vulnerability of the troops. In the United States, the vaccine was given to virtually all recruits. Between January 1941 and April 10, 1942, an astounding 7 million doses were distributed, all manufactured by the International Health Division of the Rockefeller Institute, at no charge. A strain in use in Colombia was employed, since more than 600,000 doses had been given there without serious complications, but with serum still used as a stabilizer. Eventually, 26,771 cases of jaundice, occurring 60 to 150 days after vaccination, were reported in U.S. personnel [53], and thousands more almost certainly occurred [54]. General Joseph Stilwell was among them [55]. There was a mortality of about three per 1,000 cases (the outbreak was later shown to be due to hepatitis B). The response of the press was generally quiet, perhaps recognizing the exigencies of war, but the Chicago Tribune reacted with some outrage, noting that 20 times as many soldiers had fallen victim to the vaccine as had been wounded thus far in the war. The paper called for an investigation, claiming inadequate testing and questioning the need for all soldiers to receive the vaccine [56].

There was indeed a comprehensive investigation. Almost all cases had received vaccine from a limited number of lots, and

the data indicated serum as the most likely culprit. A conscious decision to use serum as a stabilizing agent had been made on the grounds that the link between serum and jaundice was not fully established and there was too little experience using vaccine without serum stabilization to recommend it on so large a scale. The high demand for vaccine required a weekly supply of eight to 10 liters of pooled serum, and procurement of serum was the limiting factor in production. Most of it was obtained from the Johns Hopkins School of Public Health, the donors being medical students, interns, nurses, and medical technologists, all presumed healthy. Later study of donors revealed that several had prior histories of jaundice. The amount of serum in a single dose of vaccine was 0.04cc, and the infecting dose in pooled serum would have been much lower [57].

The immediate action taken was twofold: Switch to a vaccine without serum, and restrict vaccination to personnel going to or through defined areas of yellow fever risk. These measures resolved the problem, and the overall experience proved helpful in the eventual clarification of the two main types of "infectious" hepatitis. An interesting 50-year follow-up study was conducted on affected vaccinees, showing a slight increase in incidence of hepatocellular carcinoma in the non-jaundiced cases only and no increased mortality from nonalcoholic liver disease in the entire group [58].

FINAL STEPS

At the end of World War II and in the years following, the 17D and French vaccines were in use on a large scale. As the war progressed, discussion arose regarding adoption of international vaccine standards as a way to avoid quarantine. At the 1944 International Sanitary Convention for Aerial Navigation, the 17D vaccine was approved, followed by the French vaccine, given by scarification [59]. But neurologic reactions with the French vaccine were becoming more evident. An emergency vaccination campaign in Nigeria in 1953 was associated with multiple cases of encephalitis, and for the first time, vaccine virus was recovered from affected brain tissue [60]. A similar cluster of encephalitis cases occurred in Costa Rica and the Congo [44,61]. Sporadic cases of encephalitis also were being reported after the 17D vaccine, but almost all in infants.

The Pasteur Institute in Paris had begun experimenting with the 17D vaccine as early as 1936. Acknowledging its lower but adequate antigenicity vis-a-vis the French vaccines, the Institute eventually recommended it as the preferred vaccine for use in areas with appropriate technology [62]. Attempts to use the 17D vaccine by scarification were abandoned because of poor antibody production [63,64]. The demise of the French vaccine was only a matter of time, and by 1982, production of the French vaccine was discontinued [65].

In 1962, alarm bells sounded again when avian leukosis virus was detected in a seed lot of 17D vaccine in England [66] and in the United States shortly after [67], a finding of potentially disastrous proportions. These viruses, the cause of avian leukosis, displayed oncogenic activity in animals. They were widespread in the fowl population and the eggs used for virus culture. Undoubtedly, thousands or millions of people had been inadvertently inoculated with these potentially oncogenic viruses. The challenge was to eliminate the avian virus while keeping additional passages of vaccine virus to a minimum. In England, this was achieved by incubating the vaccine with antibody against avian virus, in the United States by ultrafiltration, and required only three and one extra passages respectively [68,69]. In 1972, the oncogenic issue was laid to rest with a study of 2,659 vaccinated veterans who died of cancer. Using matched controls, no evidence of excess cancer in the vaccinees was found [70].

Since 1982, the 17D vaccine, presumed clear of all contamination and manufactured from a small number of seed lots, has been the only one in use. Further developments have been of a more technical nature, such as greater stabilization of the vaccine, allowing a longer storage life [71]. The vaccines

in use today are all derived from two substrains, the 17DD and 17D-204, originally obtained from passage numbers 195 and 204, respectively, at the Rockefeller Institute. In 1985, the complete genome of the virus was published, ushering in a new era of research, both in the basic mechanisms of virus reproduction and assessing individual components for pathogenicity [72,73]. New issues include a rising incidence of severe viscerotropic disease after vaccination, most often in elderly and thymectomized individuals, and the use of the yellow fever vaccine virus as a vehicle to introduce antigens of other flaviviruses (such as dengue and Japanese B viruses), so-called "chimeric" vaccines [74].

CONCLUSION

The road to the current vaccine was bumpy and sometimes convoluted. The problems of attenuation of the virus in tissue culture, its large scale manufacture in eggs, and elimination of contaminants all pushed the limits of scientific knowledge of the time. For his efforts in extending these frontiers, Theiler was awarded the Nobel Prize in 1950, after only three nominations (apparently a low number) [75]. After his long service at the Rockefeller Institute, he was appointed professor of Epidemiology and Public Health at Yale University Medical School from 1964 to 1967, and he died in 1972.

The earlier dream of eliminating yellow fever from the earth by mosquito control died with the discovery of the jungle cycle. Vaccination still provides an essential, though often underutilized, mode of protection. World Health Organization programs for the laboratory detection of yellow fever outbreaks and the dispensation of vaccine for both preventive and emergency uses (in conjunction with the Global Alliance for Vaccines and Immunization) are now in effect [76]. The modern vaccine, though not perfect, plays a major role today in preventing and/or interrupting outbreaks of "yellow jack," once the scourge of so many communities.

REFERENCES

1. Sternberg GM. Report of the Etiology and Prevention of Yellow Fever. Washington: Government Printing Office; 1890. p. 49-65.
2. Manson P. Tropical Diseases. A Manual of the Diseases of Warm Climates. 1st ed. London: Cassell & Co.; 1898. p. 127.
3. Reed W, et al. The etiology of yellow fever. An additional note. J Amer Med Assoc. 1901;36:431-40.
4. Yellow fever. A compilation of various publications. Results of the work of Maj. Walter Reed, Medical Corps, United States Army, and the Yellow Fever Commission. 61st Congress, 3rd session. Senate Doc No 822. Washington: Government Printing Office; 1911.
5. Guiteras J. Experimental yellow fever at the inoculation station of the Sanitary Department of Havana with a view to producing immunization. American Medicine. 1901;3:809-17.
6. Noguchi H. Etiology of yellow fever: II. Transmission experiments on yellow fever. J Exp Med. 1919;29:565-84.
7. Noguchi H. Etiology of yellow fever: V. Properties of blood serum of yellow fever patients in relation to Leptospira icteroides. J Exp Med. 1919;30:9-12.
8. Noguchi H. Etiology of yellow fever: IX. Mosquitoes in relation to yellow fever. J Exp Med. 1920;30:401-10.
9. Noguchi H. Etiology of yellow fever: X. Comparative immunologic studies on Leptospira icteroides and Leptospira icterohemorrhagiae. J Exp Med. 1920;31:135-58.
10. Sorel F. La vaccination anti-amarile en Afrique Occidentale Francaise mise en application du procédé de vaccination Sellards-Laigret. Bull Off Internat d'Hyg Publique. 1936;28:1325-56.
11. A two dose vaccine given at the Broad Street Hospital, NYC. New York Times. 1920 Dec 10.
12. Noguchi H, Pareja W. Prophylactic Inoculation against Yellow Fever. J Amer Med Assoc. 1921;76:96-9.
13. Noguchi H. Prophylaxis and Serum Therapy of Yellow Fever. J Amer Med Assoc. 1921;77:181-5.
14. Lebredo MG. Considerations suggested by publications of Dr. Noguchi on experimental yellow fever — with appendix. Trans Amer Soc Trop Med. 1919;19:499-512.
15. Agramonte A. Some observations upon yellow fever prophylaxis. Proc Internat Conf on Health

Problems in Tropical America. Kingston, Jamaica; 1924. p. 201-227. Reprinted in J Trop Med and Hyg. 1924;27:285-7.

16. Theiler M, Sellards AW. The relationship of L icterohemorrhagicae and L. icteroides. Amer J Trop Med. 1926;6:383-402.

17. Hudson NP. Adrian Stokes and yellow fever research. Trans Roy Soc Trop Med Hyg. 1966;60:170-4.

18. Plesset IR. Noguchi and his Patrons. London: Fairleigh Dickinson University Press; 1980.

19. Williams G. The Plague Killers. New York: Charles Scribner's Sons; 1969. p. 226-49.

20. Dolman CE. Hideyo Noguchi (1876-1928): His final effort. Clio Medica. 1977;12:131-45.

21. Stokes A, et al. The transmission of yellow fever to Macacus rhesus, Preliminary note. J Amer Med Assoc. 1928;90:253-5.

22. Theiler M, Sellards AW. The immunological relationship of yellow fever as it occurs in West Africa and in South America. Ann Trop Med Parasitol. 1928;22:449-60.

23. Vargues R. Hommage a Jean Laigret: La petite histoire de la découverte de la vaccination contre la fièvre jaune. Presse Medicale. 1966;74:2441-2.

24. Sellards W, Mathis C, Laigret J. Sensibilité du Macacus rhesus au virus de la fièvre jaune. CR Acad Sci. 1928;186:604-6.

25. Ducloux M. Francois Miyeli (1911 – 1927 – 1973) et la souche francaise amarile. Bull Soc Med Afr Noire Lang Franc. 1975;20:174-9.

26. Sellards AW, Hindle E. The Preservation of yellow fever virus. Brit Med J. 1928;1:713-14.

27. Hindle E. An experimental study of yellow fever. Trans Roy Soc Trop Med. 1929;22:405-34.

28. Andervont HB. Activity of herpetic virus in mice. J Infect Dis. 1929;44:383-93.

29. Theiler M. Studies on the action of yellow fever virus on mice. Ann Trop Med Parasit. 1930;24:249-72.

30. Williams G. The Plague Killers. New York: Charles Scribner's Sons; 1969. p. 260-1.

31. Berry GP, Kitchen SF. Yellow Fever accidentally contracted in the laboratory. Amer J Trop Med. 1931;11:365-434.

32. Theiler M, Smith HH. Use of yellow fever virus modified by in vivo cultivation for human immunization. J Exper Med. 1937;65:787-800.

33. Strode GK, editor. Yellow Fever. New York: McGraw-Hill Book Co.; 1951. Chapter 2.

34. Sawyer WA, et al. Vaccination of humans against yellow fever with immune serum and virus fixed for mice. Proc Soc Exper Biol Med. 1931;29:62-4.

35. Theiler M. Neutralization tests with immune yellow fever sera and a strain of yellow fever virus adapted to mice. Ann Trop Med Parasit. 1931;25:69-77.

36. Laigret J. La vaccination contre la fievre jaune. Arch Inst Pasteur Paris. 1934;23:413-37.

37. Sorel F. La vaccination anti-amarile en Afrique Occidentale Francaise mise en appli-cation du procédé de vaccination Sellards-Laigret. Bull Off Internat d'Hyg Publique. 1936;28:1325-56.

38. Laigret J. Au sujet des reactions nerveuses de la vaccination contre la fievre jaune. Bull Soc Pathol Exot. 1936;29:823-8.

39. Nicolle C, Laigret J. Vaccination contre la fievre jaune a l'aide d'une seule inoculation du virus amaril vivant, desséché et enrobé. Arch Inst Pasteur Tunis. 1936;25:28-39.

40. Peltier M, et al. Vaccination mixte contre la fievre jaune et la variole sur des populations indigenes du Senegal. Ann Inst Past (Dakar). 1940;65;146-69.

41. Peltier M. Yellow fever vaccination, simple or associated with vaccination against small-pox, of the populations of French West Africa by the method of the Pasteur Institute of Dakar. Amer J Pub Hlth. 1947;37:1026-32.

42. Durieux C. Mass yellow fever vaccination in French Africa south of the Sahara. In: Smithburn K, et al., editors. Yellow Fever Vaccination. Geneva: World Health Organization; 1956. p. 115-21.

43. Durieux C. Preparation of yellow fever vaccine at the Institute Pasteur, Dakar. In: Smithburn K, et al., editors. Yellow Fever Vaccination. Geneva: World Health Organization; 1956. p. 31-43.

44. Stuart G. Reactions following vaccination against yellow fever. In: Smithburn, K, et al., editors. Yellow Fever Vaccination. Geneva: World Health Organization; 1956. p. 143-189.

45. Theiler M, Smith HH. The effect of pro-longed cultivation in vitro upon the patho-genicity of yellow fever virus. J Exper Med. 1937;65:767-86.

46. Theiler M, Smith HH. The use of yellow fever virus modified by in vitro cultivation for human immunzation. J Exp Med. 1937;65:787-800.

47. Smith HH, et al. Yellow fever vaccination with cultured virus (17D) without immune serum. Amer J Trop Med Hyg. 1938;18:437-68.

48. Smith HH. Life's a Pleasant Institution: The Peregrinations of a Rockefeller Doctor. Tucson: Smith; 1978.

49. Fox JP, et al. Encephalitis in man following vaccination with 17D yellow fever virus. Amer J Hyg. 1942;36:117-42.

50. Soper FL, Smith HH. Yellow fever vaccination with cultivated virus and immune and hyperimmune serum. Amer J Trop Med. 1938;18:111-34.

51. Findlay GM, MacCallum FO. Note on acute hepatitis and yellow fever immunizaation. Tran Roy Soc Trop Med Hyg. 1937;31:297-308.

52. Fox JP, et al. Observations on the occurrence of icterus in Brazil following vaccination against yellow fever. Amer J Hyg. 1942;36:68-116.

53. Sawyer WA, et al. Jaundice in Army Person-nel in the Western Region of the United States

and its Relation to Vaccination against Yellow Fever (part I). Amer J Hyg. 1944;39:337-430.

54. Farley J. To Cast Out Disease: A history of the International Health Division of the Rockefeller Foundation. New York: Oxford University Press; 2004. p. 178.

55. Time Magazine. 1942 Aug 3:57-8

56. Editorials. Chicago Tribune. 1942 July 27 and 30.

57. Sawyer WA, et al. Jaundice in army personnel in the western region of the United States and its relation to vaccination against yellow fever (parts II, III, and IV). Amer J Hyg. 1944;40:35-107.

58. Norman JE, et al. Mortality follow-up of the 1942 epidemic of hepatitis B in the US Army. Hepatology. 1993;18:790-7.

59. Dakar yellow fever vaccine: An experiment to determine the immunizing power of yellow fever vaccine produced by the Pasteur Institute at Dakar. Epidem Inform Bull. 1946;2:618-32.

60. MacNamara FN. Reactions following neurotropic yellow fever vaccine given by scarification in Nigeria. Trans Roy Soc Trop Med Hyg. 1953;47:199-208.

61. de Marsaguet GC, Thomas J. Les etats encephalo-meninges succedant aux vaccinations antivariolique et antiamarile associees ou isolees. Med Tropicale. 1961;21:115-128.

62. Stefanopoulo GJ, Duvolon S. Réactions observées au cours de la vaccination contre la fievre jaune atténué de culture (souche 17D). Bull et Mem de la Soc Med des Hop (Paris). 1947;30-31:989-99.

63. Draper CC, Knott EG. Failure to respond to vaccination with 17D yellow fever virus by scarification, and its significance. West Afric Med J. 1964;13:78-82.

64. Dick GWA. A preliminary evaluation of the immunizing power of chick-embryo 17D yellow fever vaccine inoculated by scarification. Amer J Hyg. 1952;55:140-53.

65. Monath TP. Yellow fever vaccines: the success of empiricism, pitfalls of application, and transition to molecular vaccinology. In: Plotkin SA, Fantini B, editors. Vaccinia, Vaccination, and Vaccinology. Paris: Elsevier; 1996. p. 157-82.

66. Harris RJC, et al. Contaminant viruses in two live virus vaccines produced in chick cells. J Hygiene. 1966;64:1-7.

67. Piraino F, et al. Serologic survey of man for avian leukosis virus infection. J Immunol. 1967;98:702-6.

68. Draper CC. A yellow fever vaccine free from avian leucosis viruses. J Hyg Camb. 1967;65:505-513.

69. Tauroso NM, et al. Yellow fever vaccine I. Development of a vaccine seed free from contaminating avian leucosis viruses. Proc Soc Exp Biol Med. 1968;127:1116-20.

70. Anderson PS, et al. Yellow Fever Vaccination, avian leukosis virus, and cancer risk in man. Science. 1972;177:76-7.

71. Monath TP. Stability of yellow fever vaccine. Dev Biol Stand. 1996;87:219-25.

72. Rice CM, et al. Nucleotide sequence of yellow fever virus: Implications for flavivirus gene expression and evolution. Science. 1985;229:726-33.

73. Monath TP. Glad tidings from yellow fever research. Science. 1985;229:734-5.

74. Edelman R. Dengue vaccines approach the finish line. Clin Inf Dis. 2007:45(Suppl 1):S56-60.

75. Norrby E. Yellow fever and Max Theiler: the only Nobel Prize for a virus vaccine. J Exp Med. 2007; 204:2779-84.

76. Yellow fever in Africa and South America, 2006. Weekly Epidemiol Record. 2008;83:69-76.