

PRESIDENTIAL ADDRESS

AMERICA IN THE WORLD: 100 YEARS OF TROPICAL MEDICINE AND HYGIENE*

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It is appropriate as we meet in Philadelphia on the 100th anniversary of the American Society of Tropical Medicine and Hygiene to consider the role of yellow fever in the history of the city, society, America, and the world. Epidemics of infectious diseases regularly resulted in excess mortality in Philadelphia, the most notorious of which was the yellow fever epidemic of 1793 (Figure 1). Febrile illnesses at that time were diagnosed by the pulse rate rather than by direct measurement of fever. Intermittent fevers were considered malaria, fever with pox smallpox or chicken pox, and fever with jaundice yellow fever.

The yellow fever epidemic had its start early in July when 2,000 refugees arrived in Philadelphia from the slave revolt in Santo Domingo, West Indies. These refugees introduced the yellow fever virus into Philadelphia where the abundant *Aedes aegypti* mosquitoes served as the intermediate host and vector. In early August, illness struck with an epidemic of fever, headache, and abdominal pain accompanied by jaundice, coffee ground emesis, and hemorrhage. Many of the infections rapidly progressed to death. A contemporary Philadelphia physician, Dr. William Currie, described the illness:

“after a chilly fit of some duration, a quick tense pulse—hot skin—pain in the head, back and limbs—flushed countenance—inflamed eye—moist tongue—oppression and sense of soreness at the stomach . . . from 3, 4 or even 5 days. . . . On the febrile symptoms suddenly subsiding, they were immediately succeeded by a yellow tinge in the opaque cornea . . . black vomit . . . haemorrhages from the nose, . . . agitation, deep and distressed sighing, comatose delirium and finally death.”¹

Philadelphia at the time had approximately 50,000 inhabitants, of which half fled the city as the epidemic unfolded. Nearly one in five of those remaining would die from yellow fever before the epidemic ended in November. Washington Square, one of the grand city parks designed for Philadelphia by William Penn, was turned into a mass graveyard. Mathew Carey wrote “*the appearance of most of the grave yards in Philadelphia is extremely awful. They exhibit a strong likeness of ploughed fields.*”¹ Anecdotes from Mathew Carey illustrate both the impact of the epidemic and the resulting panic:

“A man and wife, once in affluent circumstance, were found lying dead in bed, and between them was their child, a little infant, who was sucking its mother’s breasts. How long they had laid thus, was uncertain.

The scourge of yellow fever has fallen with extreme severity on some families . . . of Godfrey Gebler’s family no less than eleven were swept off the face of the earth.

Dr. Sproat, his wife, son and daughter—Michael Hay his wife and three children—David Flickwir and five of his family—Samuel Weatherby, wife, and four grown children, are no more.

Of the very large number of persons who have fallen under this disorder, it is not improbable that a half or a third have perished merely for want of necessary care and attention, owing to the extraordinary panic.

With the poor, the case was, as might be expected, infinitely worse than with the rich. Many of these have perished, without a human being to hand them a drink of water . . .”¹

Since the rich were better able to flee the epidemic, deaths were disproportionately among the poor, with 1,334 of the 4,041 annotated burials in potters field (Figure 2).

Important insights into the natural history of the disease were afforded from the Philadelphia outbreak. This included observations of immunity (“*it has been denied that a person is twice susceptible of the yellow fever*”) and of the dense clouds of mosquitoes in Philadelphia that summer. It was also documented in 1793 that the epidemic ended as temperatures dropped in late fall, but only from the findings of the Yellow Fever Commission a century later was the interruption of mosquito transmission understood to be the reason for the epidemic’s end (Figure 3). In contrast, at the time of the 1793 epidemic yellow fever was considered to be spread person to person or through fomites, resulting often in neglect of those stricken with the disease:

“A poor man was taken sick on the road at a village not far from Philadelphia. He lay calling for water a considerable time in vain. At length an old woman brought a pitcher full, and not daring to approach him, she laid it at a distance desiring him to crawl to it which he did. After lying there about forty eight hours, he died; and his body lay in a state of putrefaction for some time . . .”¹

Carlos Finlay (1833–1915) first hypothesized that the mosquito was the means of transmission of yellow fever (Figure 4).² He was born in Cuba and his father was a Scottish doctor and his mother a Parisienne. His early schooling was in France, but his medical education was at the Jefferson Medical College in Philadelphia. While practicing medicine and ophthalmology in Havana he became fascinated with the transmissibility of yellow fever. Finlay likely read in Lancet in 1878 of Patrick Manson’s demonstration that filarial infections were transmitted by mosquitoes.³ He hypothesized that the common house mosquito transmitted yellow fever by directly injecting the blood from an infected person into an uninfected individual, much like a flying hypodermic syringe. His lack of appreciation of the need for an extrinsic incubation period in the mosquito after an infected blood meal frustrated his attempts to experimentally transmit yellow fever. In

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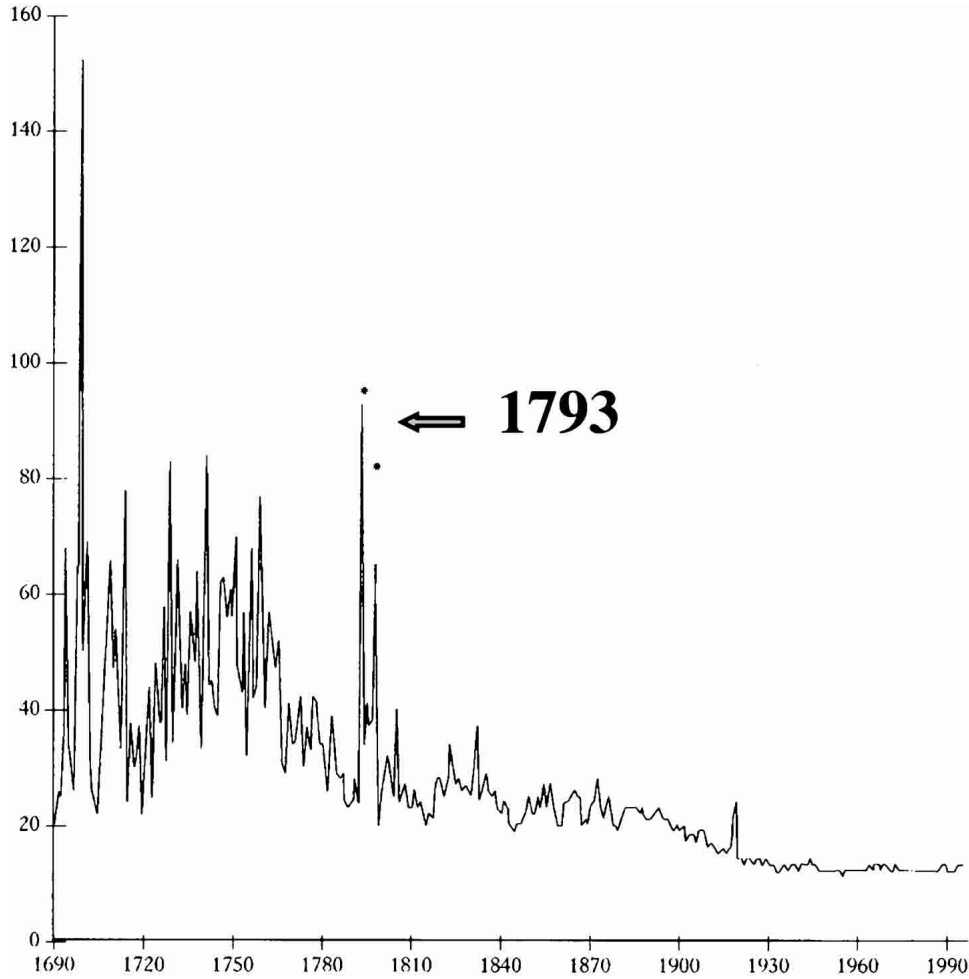


FIGURE 1. Crude death rates for Philadelphia, 1690–1990. Reprinted with permission.³⁰

a series of 104 experiments from 1881 to 1898, he attempted to transmit yellow fever to human volunteers by the bites of mosquitoes which had fed on yellow fever victims. He had hoped that such a controlled inoculation would lead to a mild case and subsequent immunity. In retrospect, at most one of the volunteers developed yellow fever and the prevailing wisdom was that Finlay has disproved his hypothesis.

After the 1793 epidemic in Philadelphia, yellow fever continued to cause sporadic outbreaks in coastal cities and towns in the United States, but reached increased prominence at the end of the 20th century. On January 25, 1898 the USS Maine entered Cuban waters. Several hundred American sailors were killed when the Maine was sunk by a mine in Havana Harbor on February 15, 1898. In the resulting Spanish-American War, yellow fever outbreaks in invasion and occupation troops spurred the formation of the Yellow Fever Commission to Cuba in 1900 (Figure 5). Then Surgeon General George Miller Sternberg (1838–1915) formed the Commission (Figure 6). Sternberg had been a member of the Chaille Commission to Havana Cuba in 1879 that met with Carlos Finlay and concluded the yellow fever was potentially caused by a living entity in the atmosphere.⁴ Sternberg appointed Walter Reed as the head of the Commission and

Protestant Episcopalians	Christ Church	-	-	-	-	173
	St. Peter's	-	-	-	-	109
	St. Paul's	-	-	-	-	70
Presbyterians	First	-	-	-	-	73
	Second	-	-	-	-	128
	Third	-	-	-	-	107
	Associate	-	-	-	-	12
	Reformed	-	-	-	-	33
Roman Catholics	St. Mary's	-	-	-	-	251
	German part of dq.	-	-	-	-	30
	Trinity	-	-	-	-	54
Friends	-	-	-	-	-	373
Free Quakers	-	-	Returned in gros.	-	-	39
German	Lutherans	-	-	-	-	641
	Calvinists	-	-	-	-	261
Moravians	-	-	-	-	r	13
Swedes	-	-	-	-	-	75
Baptists	-	-	Returned in gros.	-	-	60
Methodists	-	-	Do.	-	-	32
Univerfalists	-	-	-	-	-	2
Jews	-	-	Do.	-	-	2
Kenfington	-	-	-	-	-	169
Pottor's field, including the new ground	-	-	-	-	-	1334
						4041

FIGURE 2. Burial records for Philadelphia during the 1793 epidemic.¹

Yellow Fever Deaths & Ambient Temperatures

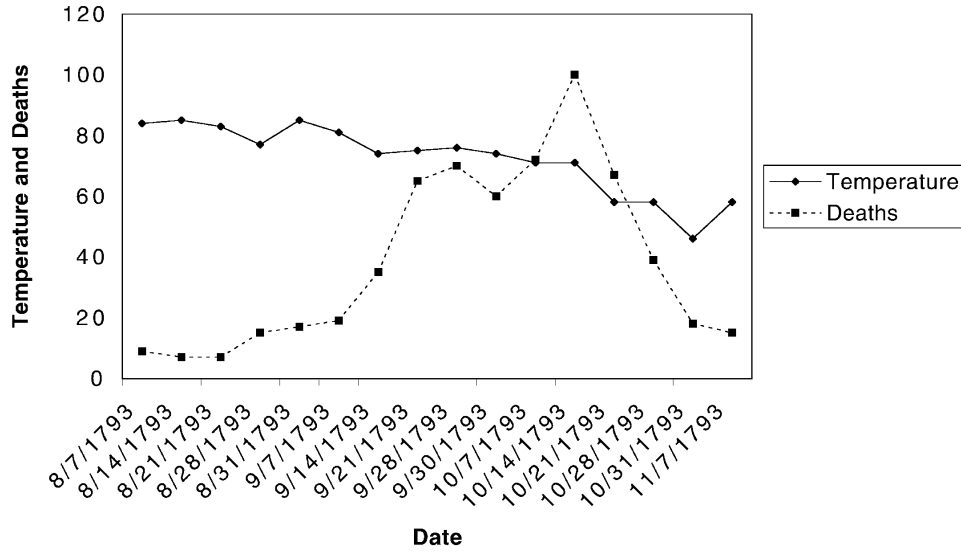


FIGURE 3. Relationship between average daily temperature and daily deaths due to yellow fever in Philadelphia, 1793.¹

Jesse Lazear, James Carroll, and Aristides Agramonte as members.

Walter Reed (1851–1902) was born in Virginia into a Methodist minister’s family (Figure 7). He moved to Charlottes-

ville after the end of the Civil War, and his mother died shortly thereafter when Reed was 14. He qualified for entrance into the University of Virginia at age 15 and received the M.D. degree at age 17, the youngest-ever graduate of the School of Medicine. After clinical training at Bellevue Hospital in New York City and epidemiologic work as a member of the New York Board of Health, he entered the U.S. Army. He was a full time practicing physician in the Army from 1874 to 1890. The year 1890 was a pivotal one in his life because he requested and received a sabbatical to the Johns Hopkins Hospital, where he worked with Sir William Osler and trained in bacteriology under William Welch. In 1893, he was appointed by Sternberg as Professor of Bacteriology at the new Army Medical School. Prior to his appointment to the Yellow Fever Commission, he served as a member of the typhoid fever board that established the importance of the human carrier state in the transmission of typhoid fever.

The second member of the Commission, James Carroll (1854–1907), was born in Woolwich, England (Figure 8). He



FIGURE 4. Carlos Finlay (1833–1915).



FIGURE 5. Burial of the dead, Cuba 1899. Hench Collection.



FIGURE 6. George Miller Sternberg (1838–1915). Hench Collection.



FIGURE 8. James Carroll (1854–1907). Hench Collection.



FIGURE 7. Walter Reed (1851–1902). Hench Collection.



FIGURE 9. Jesse Lazear (1866–1900). Hench Collection.



FIGURE 10. Aristide Agramonte (1869–1931). Hench Collection.

enlisted in the U.S. Army as a private in 1874. Through the Army he was allowed to attend medical school at the University of the City of New York, and the University of Maryland. Following receipt of the M.D. degree, Carroll studied bacteriology with William Welch at Johns Hopkins. He first worked with Reed as a hospital steward at Johns Hopkins, and later was his assistant at the Army Medical School in 1893 and the Bacteriology Laboratories at Colombian University (later named George Washington University).

Jesse William Lazear (1866–1900) was born to a wealthy family in Baltimore (Figure 9). He was a student at both Johns Hopkins and Columbia University and trained in bacteriology in Europe. Lazear served as a medical resident and later head of clinical microbiology at Johns Hopkins Hospital. Already in Cuba as an Assistant Surgeon prior to the formation of the Yellow Fever Board, in February 1900 he initiated studies on malaria and yellow fever at Camp Columbia.



FIGURE 11. Columbia Barracks in Cuba. 1900. Hench Collection.

TABLE II.

No. of Case.	Day of Disease.	Time of Autopsy.	Source of Culture.	B. Icteroides.
1	7th.	2 hours after death.	Blood, liver, spleen, kidney.	Neg' tive
2	6th.	13 hours after death.	Blood, liver, spleen, kidney.	"
3	4th.	8 hours after death.	Blood, liver, spleen, kidney.	"
4	8th.	4 hours after death.	Abdominal cavity, blood, liver, spleen, kidney, bile, duodenum.	"
5	4th.	4 hours after death.	Blood, liver, spleen, kidney, bile, duodenum.	"
6	6th.	6½ hours after death.	Abdominal cavity, blood, pericardial fluid, lung, spleen, kidney, liver, bile, duodenum.	"
7	6th.	50 minutes after death.	Blood, lung, liver, spleen, kidney, bile, jejunum.	"
8	6th.	½-hour after death.	Blood, lung, liver, spleen, kidney, urine, small intestine.	"
9	4th.	2 hours after death.	Liver, spleen, small intestine.	"
10	5th.	7 hours after death.	Liver, kidney, spleen, small intestine.	"
11	3rd.	½-hour after death.	Liver, kidney, spleen.	"

Our failure to isolate *B. icteroides* in these eleven autopsies of yellow fever patients was a result which we had not anticipated. One

FIGURE 12. Original Table II from Reed W, Carroll J, Agramonte A, Lazear JW, 1900. The etiology of yellow fever - a preliminary note.⁶

Lazear brought to the Commission experience in entomology and knowledge of Ronald Ross' work in 1897 on the role of the mosquito as an intermediate host for malaria. While in Cuba, Lazear met with Finlay and received from him



FIGURE 13. Henry Rose Carter (1852–1925). Hench Collection.

SUMMARY FOR ORWOOD AND TAYLOR.

Infecting Case.	First Secondary Case.	Interval in Days.	Secondary Cases.		People in House.	Remarks.
			Number	Days.		
Aug. 6	Aug. 23	16½	6	21½	(*) 7	Of 46 persons exposed, 45 probably contracted fever here.
Aug. 29	Sept. 13	15	3	1	(*) 4	
Aug. 29	Sept. 13	20	4	5	(*) 5	
Aug. 31 or Sept. 1	Sept. 20	19½	5	7	7	3 secondary cases occurred in 1 (the first) day.
Sept. 3	Sept. 26	23	6	10	(?)	Source of infection in last case doubtful.
Aug. 31	Sept. 22	21½	4 or 5	13 or 28	6	
Sept. 4	Sept. 20	16	2	2	(?)	Shortest interval of the list.
Sept. 2	Sept. 22	20½	1	(?)	
Aug. 29	Sept. 9	11½	1	3	
Aug. 30						Secondary case developed in 14 days.
Aug. 7	Aug. 27	20	13	27	14	
Aug. 17	Sept. 2	16	8 or 9	15	10	Paul Sisk is not rated as contracting fever at Jesse Sisk's.
Aug. 10	Aug. 25	15 or 18	3 or 2	11 or 8	5	
Aug. 11	Aug. 28					

FIGURE 14. Original summary table from Carter, HR, 1900. Interval between infecting and secondary cases of yellow fever from the records of the yellow fever at Orwood and Taylor, Miss. 1898.⁷

mosquito eggs for experimentation on yellow fever transmission.

The final member of the Commission was Aristides Agramonte (1870–1931) (Figure 10). He was born in Cuba and emigrated in 1870 to New York as an infant after his father was killed fighting against Spain. He received the M.D. from Columbia University where he was a classmate of Lazear's, and spent time as a bacteriologist with the New York City Health Department. Prior to formation of the Yellow Fever Board, he was assigned to Military Hospital #1 in Havana as pathologist in charge of the laboratories. He was thought to be immune to yellow fever from a childhood infection, and therefore performed most of the autopsies of suspected cases of yellow fever.

The military orders establishing the Yellow Fever Commission were issued on May 14, 1900: "By direction of the Secretary of War a board of medical officers is appointed to meet at Camp Columbia, Quernados Cuba for the purpose of pursuing scientific investigations with reference to the infectious diseases prevalent on the Island of Cuba" (Figure 11). This was the 4th Commission to attempt to deal with Yellow Fever along the U.S. coast and Caribbean. The Board was tasked by Sternberg with investigating the purported bacterial etiology of yellow fever described by Sanarelli. Giuseppe Sanarelli was an Italian bacteriologist who had studied at the Pasteur Institute. In 1897, working in Brazil and Uruguay, he reported the identification of *Bacillus icteroides* in 58% of the autopsies of cases of yellow fever, but almost always in association

with other bacteria. He believed that yellow fever was an intoxication due to a factor produced by *B. icteroides*. He reported that he reproduced the disease by injecting formic aldehyde-inactivated broth cultures into five humans (three of whom died).

Lazear was not interested in investigating a bacterial etiology of yellow fever and wrote to his wife on July 15, 1900 that "Dr. Reed had been in the old discussion over Sanarelli's bacillus and he still works on that subject. I am not all interested in it but want to do work which may lead to the discovery of the real organism. However I am doing as much as I can."⁵ In short order the Commission disproved *B. icteroides* as cause of yellow fever by demonstrating its absence from cultures of blood, liver, spleen, kidney, bile, and small intestine from 11 autopsied patients (Figure 12).⁶

An interested observer and seminal contributor to the Commission was Henry Rose Carter (1852–1925) (Figure 13). Carter graduated from the University of Virginia majoring in engineering. He entered the Marine Hospital Service after a leg injury prevented him from continuing as an engineer. Curious about why yellow fever could appear on a ship that had been at sea for two weeks with no antecedent sickness on board, he defined the extrinsic incubation period. Working in the Mississippi towns of Orwood and Taylor, he demonstrated that the interval between the initial and the first secondary case of yellow fever was between 15 and 23 days. In contrast, additional secondary cases occurred as early as one day after the first secondary case (Figure 14).⁷

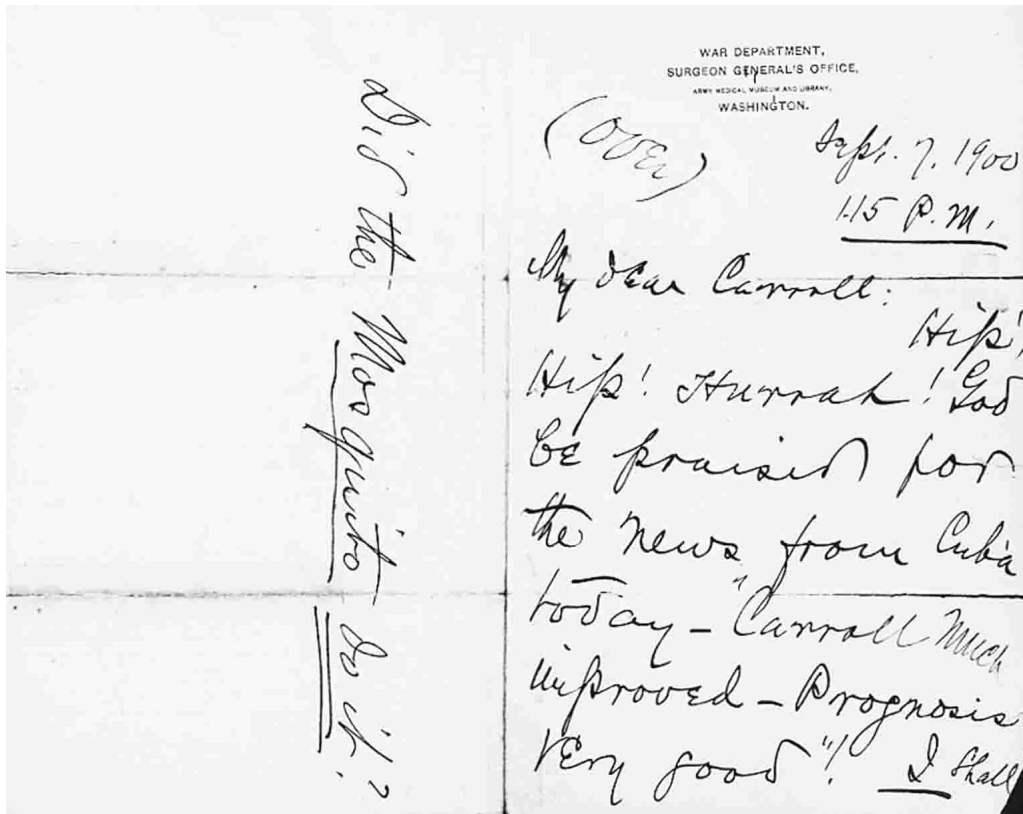


FIGURE 15. Letter from Walter Reed to James Carroll, September 7, 1900. Hench Collection.

A breakthrough occurred when Herbert Durham and Walter Myers from the Liverpool School visited Finlay and the Yellow Fever Commission in Cuba in mid-July 1900. In discussions in Cuba, Durham and Myers made the connection between the two-week extrinsic incubation period of yellow fever identified by Carter and Finlay's hypothesis that mosquitoes were the vector:

"Some means of transmission by the aid of an intermediate host—a town-loving host for this town-loving disease—is to some extent more plausible than might be anticipated."⁸

At this time, Reed first proposed human experimentation:

"There is plenty of material in Havana, with every probability of its rapid increase—our last case here died on

Monday—we will therefore expect to transfer our field of work to Military Hospital No. 1—Lazaer, Carroll and Agramonte are all deeply interested in the problem. Personally, I feel that only can experimentation on human beings serve to clear the field for further effective work—with one or two points cleared up, we could then work to so much better advantage."⁹

The Commission decided not only to experiment on humans but on themselves. According to Carroll,

"The final determination to investigate the mosquito theory was arrived at during an informal meeting of the Board (Dr. Agramonte being absent) at Columbia Barracks on the evening before Dr. Reed's departure for the United States early in August 1900. . . . The proposal to

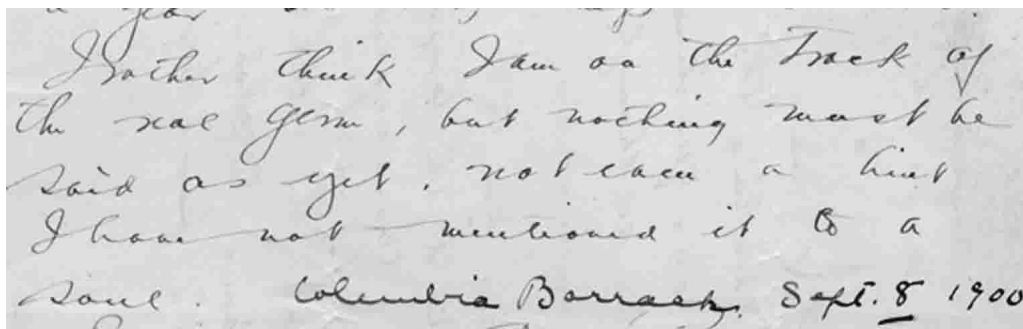


FIGURE 16. Columbia Barracks, September 8, 1900 Letter from Dr. Jesse Lazear to his wife. Hench Collection.

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2	AS	X	13	Good Samaritan 25-

RECEIVED 162 Cabot St. — Sept 26 1900

New Lazard, Atlantic Ore Beryll (Mass)

Dr Lazard died at 8 this evening

Kean

FIGURE 17. Telegram from Jefferson Randolph Kean to Mabel H. Lazard, September 26, 1900. Hench Collection.

submit ourselves to inoculation was made by myself, twice, before it was brought up by Dr. Reed, for the first time, at the meeting above mentioned, where it was finally decided upon by actual vote.”¹⁰

Immediately after this meeting, Reed departed Cuba for Washington, DC. According to Carroll: “On the evening of the 3rd of August, Reed, Lazard and I agreed to be bitten. On the following morning Reed sailed for the United States, without a word of explanation so far as I knew.”¹¹ While it is believed that Reed was summoned back to Washington to complete the report of the Typhoid Fever Commission (which in fact he did do during this visit), no military orders documenting this have been found.

Reed was in the United States as Carroll and then Lazard developed yellow fever from self-experimentation. He was remorseful to be gone while his colleagues are ill:

“I have been so ashamed of myself for being here in a safe country, while my associates have been coming down with Yellow Jack. The General has suggested that I do not return, but somehow I feel that, as the Senior member of a Bd—investigating yellow Fever, my place is in Cuba, as long as the work goes on—I shall, of course, take every precaution that I can against contracting the

disease, and I certainly shall not, with the facts that we now have allow a “loaded” mosquito to bite me! That would be fool-hardy in the extreme.”¹²

The controversy over Reed’s absence smoldered for years. After recovering from yellow fever, Carroll in a letter to his wife wrote:

“I had occasion to call at the office of the Commanding Officer today and General Baldwin, Colonel of the 7th Cavalry (Custer’s old regiment) amused me. After congratulating me upon my recovery he said suddenly, ‘By the way when is Maj. Reed coming back? I think I shall have to accuse him of running away.’” “I thought to myself you have no idea how nearly you have come to the truth.”¹³

Below the surface there was also not harmony among other members of the Commission. Lazard wrote to his wife that “Dr. Carroll is not a very entertaining person. He is a bacteriologist pure and simple. To me bacteriology is interesting only in its relation to medicine. He is interested in germs for their own sake, and has a very narrow horizon. Still good work may come out of it all. Carroll would amuse you very much. He is very tall and thin. Wears spectacles, bald headed, has a light red

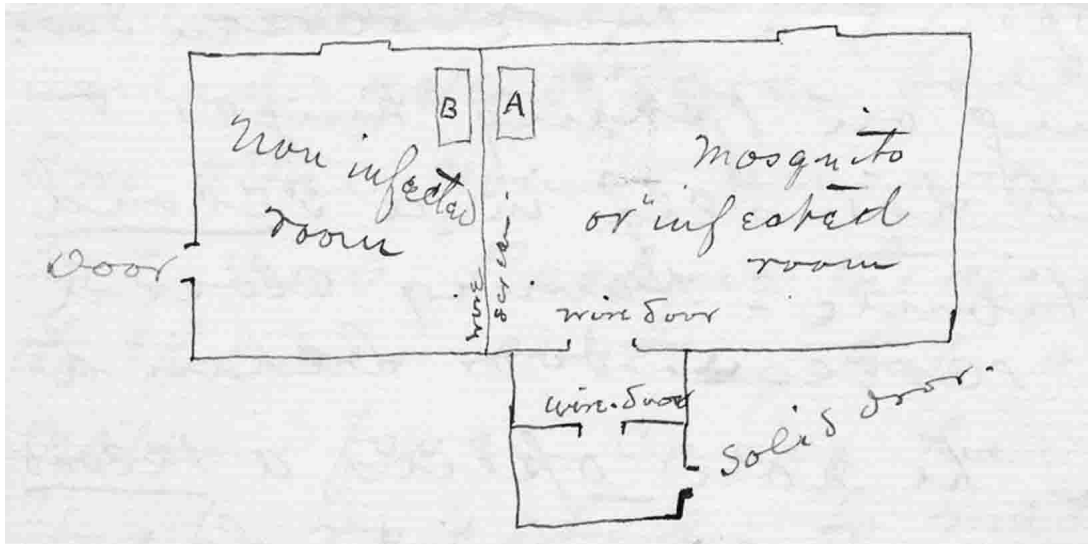


FIGURE 18. Diagram of Building 2 from letter of Walter Reed to Emilie Lawrence Reed, November 27, 1900. Hench Collection.

mustache, projecting ears and a rather dull expression."¹⁴ Carroll is concerned for years after the work in Cuba that he has received inadequate credit for the Commission's discoveries.

In Reed's absence, Lazear and Carroll began the first human experimentation to test if mosquitoes are the intermediate host. Lazear experiments on himself and eight volunteers, but none became ill as the mosquitoes had not been kept long enough after having bitten a patient with yellow fever to undergo the extrinsic incubation period. On August 27, 1900 Lazear placed a mosquito on Carroll's arm that had fed 12 days earlier on yellow fever patient. Two days later Carroll developed the symptoms of yellow fever. However, since Carroll had not taken the mosquito hypothesis seriously his infection is not properly controlled. After the mosquito had bitten him he participated in an autopsy of a yellow fever patient and traveled off post to Havana (a site endemic for yellow fever), so that when he developed yellow fever it is not

conclusive that it was from the mosquito. He recovers by September 7, 1900 but reportedly never returns to robust health.

Reed learned of Carroll's recovery while in Washington, DC and wrote "*My Dear Carroll, Hip! Hip! Hurrah! God be praised for the news from Cuba today—Carroll much improved—Prognosis very good!*" On the back of the letter Reed writes, "*Did the mosquito do it?*" (Figure 15).¹⁵

Immediately after Carroll's exposure, William Dean, a private in Troop B of the 7th Cavalry, volunteered to be bitten. He was referred to as volunteer "xy" in all records and publications because apparently he lacked permission of his commanding officer to participate in the experiments. Dean was bitten on the day that Carroll became ill with the same mosquito that bit Carroll. He suffered a mild attack of yellow fever and recovered. Dean's infection was more clearly controlled than Carroll's as Dean had not traveled from Camp Columbia in the preceding two months.⁶



FIGURE 19. Building 1 (fomites) at Camp Lazear. Hench Collection.

By September 8, Lazear was convinced of the role of the mosquito in transmission. He wrote to his wife: *"I rather think I am on the track of the real germ, but nothing must be said as yet, not same a hint I have not mentioned it to a soul"* (Figure 16).¹⁶ On September 13, 1900, Lazear allowed himself to be bitten again and by September 18, 1900, he developed fever. On September 22, he had black vomit and died on September 25. Carroll wrote that *"I will never forget the expression of alarm in his eyes when I last saw him alive on the 3rd or 4th day of his illness."* Walter Reed wrote on October 6th that:

*"Dr Lazear contracted the disease at the yellow fever hospital in Havana by letting an infected mosquito bite him—He saw the insect on his hand and deliberately let it get its fill of blood in order to test our theory—Five days later he had his chill, followed by high fever—His case was a very severe one from the beginning, his death occurring on the 6th day there after—He was a splendid, brave fellow and I lament his loss more than words can tell; but his death was not in vain—His name will live in the history of those who have benefited humanity."*¹⁷

Mabel Lazear was unaware that her husband was ill until she received a telegram from Jefferson Kean, Havana's chief sanitary officer, on September 26th stating that *"Dr. Lazear died at 8 this morning"* (Figure 17). She wrote in November to James Carroll that she was *"anxious to know more about these circumstances as to how Dr Lazear contracted yellow fever. In a note from General Wood yesterday he writes that Dr Lazear allowed a mosquito to bite him that had just bitten a yellow fever patient. Is it possible Gen. Wood could be mistaken—much as I know Dr Lazear loved his work I can hardly think he could have allowed his enthusiasm to carry him so far."*¹⁸ Mrs. Lazear considered it irresponsible of her late husband to have subjected himself to self-experimentation with two young children at home, and it is only years after his death that she understands the significance of his scientific contributions.

Not one month after the death of Lazear, Reed and the surviving members of the Commission publish in the *Journal of the American Public Health Association* "The Etiology of Yellow Fever—A Preliminary Note."⁶ Preparation of the pa-

per was primarily by Reed, because Lazear had died, Carroll was on sick leave in the United States, and Agramonte was also on leave in the United States. In this hurriedly prepared but landmark paper, the authors offered evidence to disprove *B. icteroides* as the etiologic agent, presented their data on the experimental transmission of yellow fever by the bite of infected mosquitoes, identified the mosquito (with the aid of Leland Howard of the United States Department of Agriculture) as *Culex fasciatus* (later renamed *Aedes aegypti*), and showed that successful transmission required an extrinsic incubation in the mosquito of approximately 12 days. The authors acknowledged the problem with their data on mosquito transmission that only one of the three cases was properly controlled. In fact, while Lazear was still alive Reed wrote to Carroll about his concern over the lack of appropriate controls:

*"I...cannot say that any of your cases, except perhaps Dean's prove anything. If you, my dear Doctor, had prior to your bite remained at Camp Columbia for ten days, then we would have a clear case, but you didn't!"*¹⁹

The paper is remarkable not only for the speed in its publication but for the credit given to Finlay, Carter, Durham, and Myers:

*"give our attention to the theory of the propagation of yellow fever by means of the mosquito,—a theory first advanced and ingeniously discussed by Dr. Carlos J. Finlay of Havana, in 1881 . . . Other observations . . . confirmed Carter's conclusions, thus pointing as it seemed to us the presence of an intermediate host, such as the mosquito, which having taken the parasite into its stomach . . . was able after a certain interval to reconvey the infecting agent to other individuals . . . Drs. Durham and Myers, to whom we had the pleasure of submitting Carter's observations, have been equally impressed by their importance."*⁶

The lack of rigorous controls is clear to the Commission and to Sternberg. Sternberg writes to Reed:

"I am glad to know that you are in a fair way to carry on additional inoculation experiments . . . The profession



FIGURE 20. Building 2 (mosquitoes) at Camp Lazear. Hench Collection.

El que suscribe, *Antonio Benigno*
 Mayor de veinte y cinco años de edad, natural de *Cereceda*
 provincia de *Coruna* hijo de *Manuel Benigno*
 y de *Josefa Castro* hace constar por la presente que, poseo y
 ejerzco en propia y libre y libre voluntad, consciente en conciencia de los
 experimentos que con el objeto de determinar las vias de propagacion de
 la fiebre amarilla, he de en su terreno de *Corinico* que para ese efecto he
 autorizado al Secretario de la Guerra de los Estados Unidos; que de su consentimiento
 para que se lleven a cabo dichos experimentos, por las razones y
 con las condiciones que ayo se expresan.

El infrascripto constando perfectamente bien que en el caso de concurrir
 en él la fiebre amarilla, no de sellarse de vida hasta cierto punto
 pero estando completamente imposible evitar el contagio durante su enfermedad
 en esta isla, quiere expresar la voluntad de experimentar el contagio ex-
 traordinario, con la seguridad de que se le recibirá de la Comision y sus asociados, los
 cuidados que precisa y la asistencia médica que requiere.

Quando concluido que al terminar esos experimentos, antes de transcurrir
 ochenta dias de esta fecha, el infrascripto se le recibirá la suma de \$ 100...
 Cien Americanos y que caso de declararse en él la fiebre amarilla, en cualquier
 época durante su permanencia en este Campamento, recibirá además de otras
 cantidades, otra suma de \$100. --Cien Americanos, además de su curso de y que
 caso de su aislamiento por motivo de sus enfermedades, la Comision entregará
 dicha cantidad, (o cantidad de cien Americanos,) a la persona que él en este
 momento designará al infrascripto.

El infrascripto se compromete a no salir de los límites de este Campa-
 mento durante el período de los experimentos y perderá todo derecho a los
 beneficios de este contrato si incurre en este compromiso.

Y hace su consentimiento libre esta por publicado en el Campamento Experi-
 mental, cerca de los Desamparados, el día *26* de *Noviembre*
 de mil novecientos.

El infrascripto,
Antonio Benigno
 De conformidad, la Comision.
Luigi (Rac?)
Prof. de San. U.S.A.

FIGURE 21. Informed consent form, November 26, 1900. Hench Collection.

generally will not be disposed to accept the experiments already published as definitely settling the question as to the role of the mosquito in the transmission of the disease.”²⁰

Within a month of the preliminary studies reported in the *Journal of the American Public Health Association*, Reed had planned a carefully controlled set of experiments to test the role of mosquitoes and fomites in the transmission of yellow fever. Reed wrote to his wife that “*I am having two small houses constructed—I don’t know whether I have told you this already—one for mosquito-bitten patients, and the other for testing the clothing infection theory—but I don’t want to try the latter until I have succeeded or failed with the former. Another week, I hope, will enable us to tell what mosquitoes can do, as we now have some insects that bit yellow fever cases 10 days ago today—If we can get them to live 8 or 10 days more, I believe we can reproduce the disease promptly*” (Figures 18–20).²¹

Informed consent (in English or Spanish as appropriate) was obtained for all volunteers (Spanish volunteers only)

were required to be 25 years of age or older, since that was the age of the majority in Spain. The first informed consent document for human experimentation was created for the new studies (Figure 21). It read in part (for the subject Antonio Benino):

“The undersigned, Antonio Benino being more than twenty-five years of age, native of Cerceda, in the province of Corima, the son of Manuel Benino and Josefa Castro here states by these presents, being in the enjoyment and exercise of his own very free will, that he consents to submit himself to experiments for the purpose of determining the methods of transmission of yellow fever... The undersigned understands perfectly well that in case of the development of yellow fever in him, that he endangers his life to a certain extent but it being entirely impossible for him to avoid the infection during his stay in this island, he prefers to take the chance of contracting it intentionally in the belief that he will receive from the said Commission the greatest care and the most skillful medical service.”



FIGURE 22. Hospital Corps of Camp Columbia, Cuba, September 1900. 1 = Truby (Commander); 2 = Jermerlan (blood); 3 = West (mosquitoes); 4 = Sontag (mosquitoes); 5 = Andrus (blood); 6 = Cook (fomites); 7 = Kissinger (mosquitoes). Numbers are under the faces of the identified individuals. Hench Collection.

Volunteers were paid \$100 in gold coins, with an additional \$100 provided to them or their surviving relative if they contracted yellow fever (Figure 22).

The definitive experiments were conducted at “Camp Lazear” built on the rolling fields of the Finca San Jose, on the farm of Dr. Ignacio Rojas, who leased the land to the Americans. Reed controlled all of the important variables. The area surrounding Camp Lazear was free of naturally transmitted yellow fever. Volunteers were subjected to quarantine and medical observation prior to challenge with mosquitoes to ensure that they were not incubating the disease. Finally mosquitoes were raised from eggs so as to be sterile prior to feeding on yellow fever patients.

The fomite experiments involved three volunteers in Building Number 1. It was constructed with interlocking boards and shuttered windows so as to be impervious to mosquitoes. Each evening volunteers slept in bedding that was intentionally contaminated with the vomit, feces, blood, and urine of yellow fever patients. Almost every evening newly contaminated clothing and bedding was unpacked by the volunteers who then tried to sleep amid the filth.

The mosquito experiments were conducted in Building Number 2, which had a screen dividing it approximately in half. This design allowed for mosquitoes to bite volunteers on one side of the screen while other volunteers resided on the mosquito-free part of the building.

The Camp Lazear experiments were a resounding success. Five of six volunteers developed yellow fever after being bitten by mosquitoes that had fed greater than 12 days earlier on patients in first three days of illness. “*An interval of about 12 days or more after contamination appears to be necessary before the mosquito is capable of conveying the infection.*” Volunteers on the other side of the screen (without mosquitoes) did not contract disease: “*A house may be said to be infected with Yellow Fever only when there are present within its walls contaminated mosquitoes capable of conveying the parasite of this disease.*” None of the three volunteers developed yellow fever who slept for 20 consecutive nights in the fomite house: “*Yellow fever is not conveyed by fomites, and hence disinfection of articles of clothing, bedding or merchandise supposedly contaminated by contact with those sick with this disease is unnecessary.*”

Reed, Carroll, and Agramonte conclude in their paper “The Etiology of Yellow Fever, An additional note” in 1901 that “*The spread of yellow fever can be most effectively controlled by measures directed to the destruction of the mosquitoes. . . .*”²²

The carefully conducted studies at Camp Lazear had an immediate impact on public health practices. On December 13, 1900 William Crawford Gorgas (1854–1920) wrote to Carter that “*Reed and his Board are making most extensive experiments in the line of Finlay’s mosquito theory, and in the line of Reed’s preliminary report. Evidence seems to point very strongly to the mosquito being the transmitter of the disease. There was so much evidence against it that I was not at all impressed with the few cases reported in his original article but his experiments since, have about convinced me*” (Figure 23).²³ Gorgas applied the results of the Yellow Fever Commission by launching a mosquito eradication campaign that resulted in the elimination of yellow fever as a serious threat in Cuba within six months, and later to a mosquito control program



FIGURE 23. William Crawford Gorgas (1854–1920). Hench Collection.

led by Gorgas that enabled the successful building of the Panama Canal.

It was in Delmonico’s Restaurant in Havana on December 22, 1900 that a grand celebration was held to commemorate the proof of mosquito transmission from the Camp Lazear experiments. Finlay was honored for hypothesizing the mosquito’s role, and the Yellow Fever Commission for proving it. Reed and Agramonte attended but not Carroll as he stated that he “*had no evening dress and no blue uniform to wear.*”²⁴

Walter Reed wrote to his wife Emilie Lawrence Reed on December 31, 1900:

“11:50 P. M. Dec. 31st 1900—Only 10 minutes of the old Century remain, lovie, dear. Here I have been sitting reading that most wonderful book—La Roche on Yellow fever—written in 1853—Forty-seven years later it has been permitted to me & my assistants to lift the impenetrable veil that has surrounded the causation of this dreadful pest of humanity and to put it on a rational & scientific basis—I thank God that this has been accomplished during the latter days of the old century—May its cure be wrought out in the early days of the new century! The prayer that has been mine for twenty or more years, that I might be permitted in some way or sometime to do

something to alleviate human suffering, has been answered!"²⁵

Walter Reed and James Carroll went on to demonstrate that the yellow fever agent was present in the blood of patients in the first three days of illness and that it was filterable (and therefore not a parasite or bacteria) but inactivated by heating to 55°C for 10 minutes (and therefore not likely a toxin, since tetanus toxin for example was stable at 55°C for 1.5 hours). They concluded "the important questions which naturally arise from the forgoing experiments must be left for the future observations to determine."²⁶ It was only 35 years later that Max Theiler and Hugh Smith demonstrated the usefulness of the attenuated 17D strain of yellow fever virus as a vaccine.²⁷

On December 7, 1903, the American Society of Tropical Medicine elected as the first Honorary Members Aristides Agramonte, James Carroll, William Gorgas, George Sternberg, and William Welch. James Carroll spoke at the first public meeting of the Society at the University of Pennsylvania on January 9, 1904 on "The Etiology of Yellow Fever." William Gorgas became the 4th President of the Society. The first recipient of the Walter Reed Medal ("to recognize distinguished accomplishments in the field of tropical medicine") was Emilie Lawrence Reed, and in 1942 the posthumous recipient was Carlos Finlay.²⁸

I have found the history of yellow fever to be compelling for what it teaches about the successful conduct of tropical diseases research. Foremost, rigorously conducted and controlled experiments convinced the scientific and public health community of the primary role of the mosquito in transmission. This changed hygienic policy almost overnight and eliminated yellow fever as a serious public health threat from Cuba in a matter of months.

Second, scientific interchange between developing and developed world scientists, and between scientific disciplines as different as entomology, bacteriology, and epidemiology, provided the broad perspectives and approaches that led to solution of the puzzle of transmission. Scientific communication through international journals and meetings, in letters, and in person catalyzed what were at times revolutionary insights. The establishment of a field site in a yellow fever endemic area where investigators could study the disease was central to this interchange.²⁹ Personality clashes were inevitable among the diverse investigators drawn to the study of yellow fever, but ultimately the shared objectives and motivations of the individuals yielded scientific unity.

Third, human experimentation was conducted ethically and responsibly on volunteers who could voluntarily provide consent, ultimately benefit from the control of yellow fever, and who were informed of the risks.

Finally, the scientists and physicians focused their diverse talents on a disease of worldwide importance, and by so doing changed the world.

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