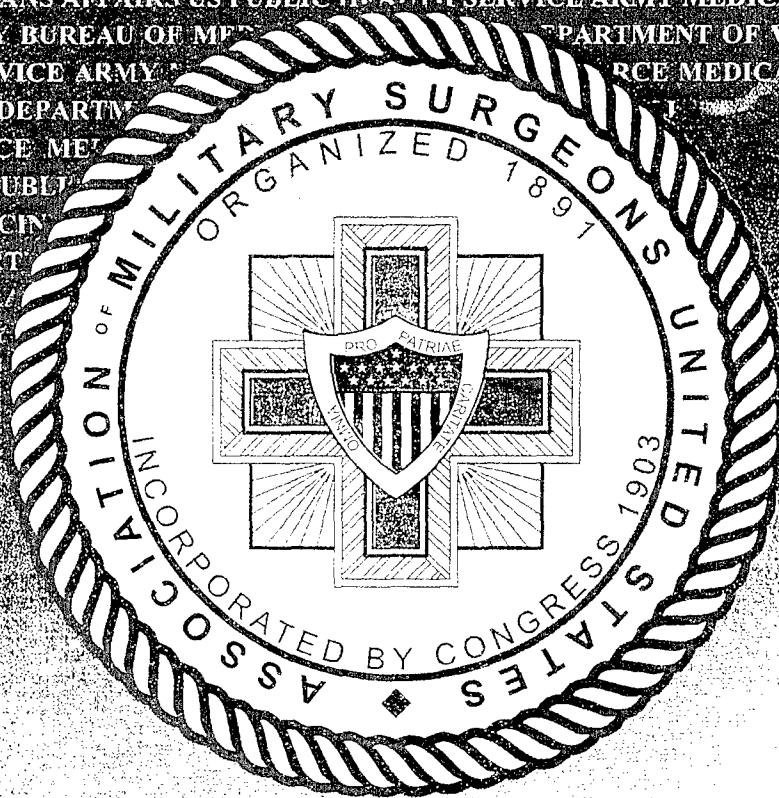


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Solving the Mystery of Yellow Fever

The 1900 U. S. ARMY Yellow Fever Board

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Editors' Note

A note to our readers: This supplement republishes the work of the U.S. Army Yellow Fever Board of 1900-1901 and several other articles that led to or followed their work. The original language, syntax, and spellings used by the original authors are, in some cases, different from what we would expect today. In addition, some of the articles have been edited for space and the historical note preceding each article will indicate when this occurred.

The Editors

Military Medicine

Solving the Mystery of Yellow Fever: The 1900 US Army Yellow Fever Board

*Sponsored by
The Walter Reed Army Medical Center
and
The Department of Defense Global Emerging Infections System
Washington, DC*

Supplement Editors

John R. Pierce, COL, MC, USA (Ret.)
James V. Writer, MPH

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MILITARY MEDICINE

VOLUME 166

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DEPARTMENT OF THE ARMY
WALTER REED ARMY MEDICAL CENTER
WASHINGTON, DC 20307-5001

REPLY TO
ATTENTION OF:

April 25, 2001

Office of the Commander

Dear Colleagues and Friends of Military Medicine:

Welcome to this special supplement of Military Medicine commemorating the 100th anniversary of the United States Yellow Fever Board of 1900-1901. Led by Major Walter Reed, this intrepid group of medical researchers participated in one of the most remarkable events in the history of the Army Medical Department. An event that reinforced our noble mission given in the Orders for the Discipline and Regulation of the Troops, 1779 that "the preservation of the soldier's health should be the commander's first and greatest care."

The purpose of this supplement is to give you the opportunity to walk in the footsteps of these extraordinary men as they planned and conducted their precedent setting research. They were assisted in their research by an equally remarkable group of enlisted men of the Hospital Corps who helped in their work as well as volunteered to participate as research subjects, risking their lives for the betterment of humanity. The supplement includes seminal articles that guided the Board to their hypotheses, the four original articles published by the members of the Board, a memoir by the last surviving member and other documents of importance and interest. I expect that you will marvel, as I have, at the extraordinary clarity of the vision and wisdom of this small group of men who, by today's standards, possessed limited training and experience in this type of clinical research. Yet, it can be said that the quality of Army medical research started with this Board.

The results of their research led to an unprecedented and extraordinary successful campaign to control mosquitoes that began in Havana in February 1901. These efforts quickly produced an almost complete eradication of yellow fever from Cuba. Application of the same principles in Panama controlled both yellow fever and malaria, literally clearing the way for the construction of the Panama Canal. This is probably the first example in history of intentionally quieting a disease by controlling its vector.

In assessing the magnitude of the benefit of their findings to the Army and to the world, General Leonard Wood, a physician and Governor General of Cuba during the work of the Board, said the discovery made by the Board "results in the savings of more lives annually than were lost in the Cuban war, and saves the commercial interest of the world a greater financial loss each year than the cost of the Cuban war." A contemporary editorial in the *Journal of the American Medical Association (JAMA 42:39, 1904)* said their work "always will remain one of the chief glories of American medicine."

September 2001 marks the 150th anniversary of the birth of Walter Reed. This remarkable American was a pioneer in medical research and education while serving much of his career as a frontier Army doctor. As such, he truly was a medical leader of competence and character who gave a lifetime of service to the Nation.

Welcome to this truly extraordinary adventure. I hope you enjoy it as much as I have.

In the service of soldiers,

A handwritten signature in dark ink, reading "Harold L. Timboe".

HAROLD L. TIMBOE
Major General, U.S. Army
Commanding



DEPARTMENT OF THE ARMY
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504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

Office of the Commanding General

Welcome to this Special Supplement

Dear Readers:

The commemoration of the research described in this special issue of Military Medicine serves two important purposes. First, it is a celebration of the work of the U.S. Army's 1900 Yellow Fever Board, which through a series of elegant experiments solved a centuries old mystery. It is also a celebration of a century of military medical research.

The success of the Yellow Fever Board's investigations, and the nearly immediate and dramatic eradication of the disease from Havana established the research credentials of the U.S. Army. It is a legacy that we strive to uphold every day at our research facilities in the United States and around the world, active duty soldiers doing medical research to the benefit of the Army as well as humanity.

The scope of military medical research is necessarily broad, covering the full spectrum of bio-medical disciplines. This includes infectious and non-infectious diseases, blood products, treatment of burns, surgical procedures, and many others. Vaccine, drugs, devices, and techniques are the products of our efforts — products whose primary customers are the men and woman of our armed forces but whose benefits are global as were the benefits of the work of the Yellow Fever Commission.

I invite you to read through the articles, letters, and other documents in this supplement. You will see that the research process has changed little in 100 years. The board borrowed from and built on previous research. They solicited the advice and support of other scientists. And, perhaps for the first time in the history of medical research, they required volunteers to give written informed consent before entering the study. The bi-lingual consent form is reproduced in this issue.

Sincerely,

A handwritten signature in cursive script, reading "John S. Parker", is positioned above the typed name.

John S. Parker
Major General, Medical Corps
Commander

MILITARY MEDICINE

ORIGINAL ARTICLES

Authors alone are responsible for opinions expressed in the contribution and for its clearance through their federal health agency, if required.

MILITARY MEDICINE, 166, Suppl. 1:003, 2001

Introduction: Yellow Fever Before 1900

At the dawn of the 21st century, yellow fever is for most physicians a medical oddity — a vaccine-preventable disease, briefly mentioned in medical school, never expected to be seen in practice, yet reported every so often from the distant tropics. Throughout the 19th century, however, yellow fever was central to disputes about contagion, the germ theory, and public health practice.¹ Scientific debate aside, for much of the U.S. population, especially those in the Southeast and port cities, yellow fever was a very real and terrifying threat.

While European explorers and traders in Africa described no such disease, it appears that both the yellow fever virus and its primary urban vector, *Aedes aegypti*, originated in central Africa.² Their spread to the New World was aided by the slave trade and commerce of the 15th through 19th centuries. The ancient Egyptians, Romans, Greeks, and Europeans of the Middle Ages have left no written record of yellow fever.³ The earliest written description of yellow fever reportedly dates to 1495, following the battle of Vego Real or Santo Cerro in Hispaniola fought between the soldiers of Christopher Columbus and the native Indians.³

Yellow fever is an acute infectious viral disease that is transmitted by the bite of a female mosquito. There are two recognized forms of the disease: an urban form carried by the *Ae. aegypti* mosquito and a jungle or sylvan form, transmitted by the *Hemagogus* species mosquito from canopy-dwelling monkeys. Humans are the primary host in the urban cycle and are a secondary host in the jungle cycle.⁴

Attacks can range from mild to fatal. Mild cases may cause flu-like or Dengue-like symptoms, including sudden onset, fever, chills, headache, backache, myalgia, prostration, nausea, and vomiting. More severe forms are characterized by internal bleeding and liver and kidney damage. Jaundice is a common feature and thus the English name yellow fever. Latin Americans named the disease after another of its more dramatic features *el vomito negro*, the black vomit. The case fatality rate ranges from 5% of the infected population in endemic areas to 50% among naïve populations during epidemics. An attack of yellow fever imparts lifetime immunity.⁵

Throughout the ensuing centuries, yellow fever was a powerfully ally of the out-gunned natives of the Caribbean basin in their struggle against European colonization. The English, French,

and Spanish lost whole armies to the disease. Almost 20% of all British soldiers sent to Jamaica died of yellow fever. While occupying Haiti, the French lost an entire garrison to yellow fever in 1 year.³

From 1702 to 1800 the disease appeared at least 35 times in the U.S. From 1800 until 1879, the U.S. had an annual yellow fever epidemic every year except two.⁶ Appearing in the spring and ending in the fall, epidemics generally began slowly with one or two cases, which then spread through the population. The apparent randomness of the infection caused terror and panic in a community. In his book *The Microbe Hunters*, Paul DeKriuf wrote, with a touch of hyperbole, "... when folks of a town began to turn yellow and hiccup and vomit black, by scores, by hundreds, everyday — the only thing to do was to get out of that town."⁷

The deadliest epidemic occurred along the Mississippi River from the Gulf of Mexico to Memphis, Tennessee in 1878. From 16,000 to 20,000 people died as yellow fever swept upstream.² The Tennessee Board of Health noted, "1878 will be remembered by the people of Tennessee as a year especially marked as one of disaster and death."¹

But an epidemic in Philadelphia in 1793 may be the most infamous. In this siege on the city over 4,000 people, 1 of every 10 citizens, died.⁸ Theories about the cause and spread of the disease abounded — it was blamed on rotting coffee grounds piled on the docks — it was declared to be contagious — it was declared not to be contagious.

Writing in *A Short Account of the Malignant Fever Lately Prevalent in Philadelphia (1793)*, Mathew Carey describes how people reacted, "Many never walked on the footpath, but went into the middle of the streets, to avoid being infected by passing houses wherein people had died. Acquaintances and friends avoided each other in the streets, and only signified their regard by a cold nod. The old custom of shaking hands fell into such general disuse, that many were affronted at even the offer of the hand."⁶

Dr. Benjamin Rush, the city's leading physician and later Surgeon General of the United States, described the epidemic in his letters.⁹ His descriptions of the fear engendered by the disease are especially poignant and chilling. In an 18 September 1793 letter to his wife he writes, "... parents desert their children as soon as they are infected, and in every room you enter you see no person but a solitary Black man or woman near the sick. Many people thrust their parents into the streets as soon as they complain of Headache."

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A week later he writes a friend, "No words can describe the distress which pervades all ranks of people from the combined operators of fear, grief, poverty, despair and death."⁹

Rush also made observations about the conditions in Philadelphia noting that mosquitoes were unusually plentiful in Philadelphia that year. He also knew that fall would bring an end to the epidemic, "O! that it were October or November for I despair under present circumstances of the disease being checked till we have frost or heavy rains."⁹

Two years later, during an epidemic in New York, Noah Webster wrote, "mosquitoes [sic] were never before known by the oldest inhabitants to have been so numerous."¹⁰

As the last years of the 19th century began, scientists and doctors knew little more about the spread and control of yellow fever than they did in the first years of the century. More importantly, they did not know what they did not know. In their ignorance some "great discoveries" had been made. In Italy, Dr. Giuseppe Sanarelli discovered what he was sure was the yellow fever bacteria; he called it *Bacillus icteroides*. In Cuba, Major William Crawford Gorgas of the U.S. Army was scrubbing centuries of filth away from the streets of Havana, certain he was scrubbing yellow fever away with it. Gorgas, although becoming discouraged by the work, would eventually defeat the disease both in Havana and Panama.

Meanwhile, in 1898, the U.S. Marine Hospital Service, forerunner of the Public Health Service, said, in what may have been the last official pronouncement on the spread of yellow fever before Walter Reed's work in Cuba, "While yellow fever is a communicable disease, it is not contagious in the ordinary acceptance of the term, but is spread by the infection of places and articles of bedding, clothing, and furniture."⁶ This was called the fomite theory, which stated that anything a yellow fever victim touched was potentially contagious.

The Spanish-American War in 1898 gave the U.S. a permanent presence in the Caribbean and an opportunity to come face to face with the scourge. It was long suspected that the yellow fever attacking U.S. cities, especially the seaports, originated in the Caribbean with Cuba as a foci of contagion.⁶ It was thought that yellow fever was an unfortunate and deadly consequence of commerce; little could be done to protect the U.S. other than inspection and quarantine of ships and their cargo.

The U.S. had to find a way to control yellow fever. "The man who conquers yellow fever would be the real conqueror of Cuba," wrote Marie Gorgas, wife of Major William Gorgas.¹⁰ As a survivor of a yellow fever attack, Gorgas could study and work with the disease with impunity, which was one of the reasons he was sent to clean-up Havana after the war. Gorgas, trusting in the fomite theory, wrote, "Let me give [Havana] a good scouring and a bath. . . and yellow fever and other diseases will disappear."¹⁰ Gorgas did his job well; "[Havana] had become as orderly, as clean, and as civilized in its appearance as Fifth Avenue."¹⁰ Yellow fever subsided at first but then came on with a vengeance.

In the spring of 1900, yellow fever was epidemic in Havana and elsewhere in Cuba. Following the war, a newly stabilized Cuba was inundated by Spanish immigrants seeking a new life. Between August and December of 1899 over 12,000 disembarked.¹⁰ In addition, military and civilian personnel from the U.S. had a large presence. Unlike most Cuban natives, the newcomers had never been exposed to yellow fever and were not

immune to it. They unwittingly provided the fuel for an explosion of cases. One-third of the Army's staff officers contracted the illness. At an officers' mess of eight men an old English toast was resurrected, "To those who are gone already and here's to the next to go!"¹¹ Overall, there were 1,200 reported cases in 1900.⁶ "[T]he disease is worse than I ever knew it to be," said General Fitzhugh Lee, Consul-General of Cuba.¹² The New York Times noted, "Houses in which the sanitation is excellent seem to harbor it and theories that is caused by unsanitary conditions must be thrown aside. . . and others sought."¹³

Earlier in his career Army Surgeon General George Miller Sternberg had battled yellow fever in New York, Florida, and elsewhere; he had served on several scientific commissions investigating its etiology. He once claimed (and later rescinded his claim) that he had found the germ that caused the disease. In May 1900, in response to the worsening condition in Cuba he recommended the creation of a board of medical officers to pursue "scientific investigations with reference to the infectious diseases prevalent on the Island of Cuba and especially of yellow fever."¹⁴ When the special order establishing the medical board was written yellow fever was not mentioned.¹⁵ In a letter from Sternberg to Walter Reed several days later, however, the Surgeon General wrote, "You will naturally give special attention to questions relating to the etiology and prevention of yellow fever."¹⁶ The Board's mission to find the cause of the disease was clear.

Major Walter Reed, was named board chairman. Other members of the board were contract surgeons, James Carroll, Jesse Lazear, and Aristides Agramonte. Lazear and Agramonte were already in Cuba. Reed and Carroll left Washington in late June 1900 to join them.

What follows in this supplement to *Military Medicine* is a recounting of the board's scientific investigations through original articles, letters, and other documents.

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Biography of Dr. Carlos Juan Finlay

Carlos Juan Finlay was born in Cuba on December 3, 1833. His physician father was a Scotsman who owned a coffee plantation; his mother was a native of France. At age 11, he went to Europe to study but had to return home on two occasions because of illness. After he recovered from typhoid, his second illness, he decided to go to the U.S. to study medicine, and he enrolled in Jefferson Medical College where he graduated in 1855. He practiced in a small town in northwest Cuba but moved to Havana where he found the practice and life style more suitable. Over the years he became interested in the problems of public health, especially yellow fever.

In 1879 the U.S. Yellow Fever Commission arrived in Havana to study yellow fever, and he was named as the representative of the Cuban government. Also on the commission was Major George Miller Sternberg, the U.S. Army's leading expert on yellow fever. Finlay originally thought that yellow fever was due to the strongly alkaline atmosphere of Havana, but work with the commission changed his thoughts and he became intrigued with the idea that the mosquito transmitted yellow fever. Sternberg and the others did not agree.

In 1881 he presented his theory before the Academy of Sciences of Havana in a paper titled "The Mosquito Hypothetically Considered as the Agent of Transmission of Yellow Fever." His careful observations had led him to believe that the female Culex mosquito (later called *Stegomyia* and now known as *Aedes*) was "the intermediate agent in the transmission of yellow fever." Over the next 20 years, Finlay repeatedly failed in over 100 attempts to transmit yellow fever to human volunteers by the bites of his mosquitoes, never producing an unmistakable case. Others had proposed this idea previously but Finlay was the first to conduct experiments on the theory. He was derisively called by some "the mosquito man," but he strongly persisted in his belief.

After the destruction of the battleship U.S.S. Maine in Havana harbor on February 15, 1898, the U.S. demanded that Spain withdraw from Cuba. Spain responded by declaring war on the U.S.; the U.S. Congress reciprocated on April 25, 1898. Finlay was in Tampa at the time and offered his services to his old friend George Miller Sternberg, now Surgeon General of the U.S. Army. Although Finlay was 65 years old, Sternberg accepted, and Finlay was sent to Santiago de Cuba as an assistant surgeon. After the brief war he was discharged and returned to

Havana. He was named the head of the Havana Yellow Fever Board, whose membership included Dr. Henry R. Carter of the U.S. Marine Hospital Service and Major William C. Gorgas, U.S. Army.

After the early work of the U.S. Army Yellow Fever Board had resulted in unsuccessful attempts to identify the etiological agent of yellow fever, they turned to Dr. Finlay to discuss with him the possibility of the mosquito as the agent of transmission. He received them eagerly and shared with them some of this mosquito larvae from which they grew the initial mosquitoes used in their experiments.



Historical Background: Dr. Carlos Finlay read this paper before the Royal Academy of Medical, Physical, and Natural Sciences at Havana, Cuba on August 14, 1881. The original report was published in *Anales de la Ciencir Medicas, Fisicas y Naturales de la Habana*, Vol. XVIII, pare 147. The version presented here was translated by Dr. Carlos J. Finlay and was published in *Trabajos Selectos del Dr. Carlos J. Finlay*, Secreteria de Sanidad y Beneficencia, Republica de Cuba, Habana, 1912, pages 27-43. In the paper Dr. Finlay presented a well thought out but largely ignored, if not openly ridiculed, theory of yellow fever transmission by the *Culex* (now *Aedes aegypti*) mosquito. The theory was based on his observations of the epidemiology of yellow fever and the ecology and structure of the mosquito. For nearly 20 years Dr. Finlay tried to prove his theory. He was still trying when the U.S. Army's Yellow Fever Board convened in Cuba in 1900. Dr. Finlay provided the first mosquitoes used by the Board. The paper has been edited for space and readability; footnotes were deleted. An ellipsis (. . .) indicates where text has been deleted from the article. Three asterisks (***) indicate where a paragraph(s) has been deleted. The illustration was omitted.

The Mosquito Hypothetically Considered as the Agent of Transmission of Yellow Fever

Carlos Juan Finlay, MD

Mr. President, Gentlemen.-

Some years ago I had the honor to submit to your consideration the results of my alkali-metric experiments, by which I think I have definitely demonstrated the excessive alkalinity which prevails in the atmosphere of Havana. Some of the Members now present, may perhaps remember the relations which I then attempted to establish between that peculiarity and the development of yellow fever in Cuba. Much however has been done since that time, more accurate data have been obtained, and the etiology of yellow fever has been more methodically studied. In consequence thereof I feel convinced that any theory which attributes the origin and propagation of yellow fever to atmospheric influences, to miasmatic or meteorological conditions, to filth or to the neglect of general hygienic precautions, must be considered as utterly indefensible. I have, therefore, been obliged to abandon my former ideas, and shall now endeavor to justify this change in my opinions, submitting to your appreciation a new series of experiments which I have undertaken for the purpose of discovering the manner in which yellow fever is propagated.

In this paper I shall not concern myself with the nature or form of the morbid cause of yellow fever, beyond postulating the existence of a material, transportable substance, which may be an amorphous virus, a vegetable or animal germ, a bacterium, etc., but, at any rate, constitutes something tangible which requires to be conveyed from the sick to the healthy before the disease can be propagated. What I propose to consider is the means by which the morbid cause of yellow fever is enabled to part from the body of the patient and to be implanted into that of a healthy person. The need of an external intervention, apart from the disease itself, in order that the latter may be transmitted is made apparent by numerous considerations; some of them already pointed out by Humboldt and Benjamin Rush since the beginning of this century, and now corroborated by recent observations. Yellow fever, at times, will travel across the Ocean to be propagated in distant ports presenting climatic and topographic conditions very different from those of the focus from which the infection has proceeded, while, at other times, the disease seems unable to transmit itself outside of a very

limited zone, although the meteorology and topography beyond that zone do not appear to differ very materially. Once the need of an agent of transmission is admitted as the only means of accounting for such anomalies, it is evident that all the conditions which have hitherto been recognized essential for the propagation of the disease must be understood to act through their influence upon the said agent. It seemed unlikely, therefore, that this agent should be found among Micro or Zoophytes, for those lowest orders of animal life are but little affected by such meteorologic variations as are known to influence the development of yellow fever. To satisfy that requisite it was necessary to search for it among insects. On the other hand, the fact of yellow fever being characterized both clinically and (according to recent findings) histologically, by lesions of the blood vessels and by alterations of the physical and chemical conditions of the blood, suggested that the insect which should convey the infectious particles from the patient to the healthy should be looked for among those which drive their sting into blood-vessels in order to suck human blood. Finally, by reasons of other considerations which need not be stated here, I came to think that the mosquito might be the transmitter of yellow fever.

Such was the hypothesis which led me to undertake the experimental investigation which I shall here relate.

Let us first recall the geographical distribution of mosquitoes. They may be said, in general terms, to exist everywhere, except at great altitudes above the sea-level. Many believe that the dipterous insect with which we are concerned, the genus "*Culex*," constitutes a special torment of the tropical regions, while in reality it is found in all latitudes. In the polar regions, the Laplanders, just as the inhabitants of the equinoctial regions of America, are prevented from taking their meals and from lying down to sleep within their huts, unless they surround themselves with an atmosphere of smoke in order to escape those pests. In the open, those insects will fly into their mouths and nostrils, and, notwithstanding the hardening of their skin during the previous winters, they find it necessary to use veils steeped in fetid grease and to anoint their bodies with cream or

lard as a protection against mosquitoes. In Canada, in Russia, in England, in France, in Spain, all over Europe, in Siberia, China, the United States, in North and South America, mosquitoes abound. In Central Africa, a German explorer, Dr. Schwinfurst, was tormented by a "spotty-legged" species whose description might agree with that of the Cuban *C. Mosquito*; and perhaps also the species observed in Batavia by Arnold, as stated by Dr. Kirby, who considers it as a nondescript variety, not unlike the *C. annulatus*, but without any spots on its wings.

Although mosquitoes are found in all latitudes, their abundance varies in different localities. Humboldt and Bonpland, in their *Travels in Equinoctial America* wrote: "The annoyance suffered from mosquitoes and "zancudos" in the torrid zone is not so general as most people think. On the high plateaux more than 400 toises (2500 feet) above the sea-level, and in very dry plains, far from large rivers, such as Cumana and Calabozo, gnats are not much more abundant than in the most populous parts of Europe." The influence of dryness and of a long distance from water-courses, pointed out by those travelers, is easily understood, inasmuch as the larvae and pupae of the mosquitoes are aquatic, and the winged insect requires water for the laying and hatching of its eggs. The impediment to their propagation at high levels may consist in the exaggeration of the difficulty which those insects must always experience in flying upwards after they have filled themselves with blood; a difficulty which will be much more marked in a species having such small wings as those of the *C. mosquito*. The rarefaction of the atmosphere at those great heights necessarily increases that difficulty, and, under those circumstances, the mosquito will instinctively shun those localities. The above mentioned travelers also relate that a missionary priest, Bernardo Zea, had built himself a room over a scaffolding of palm boards, and they used to go there at night to dry their plants and to write their Diary, adding: "The missionary had rightly observed that those insects are more numerous in the lower strata of the atmosphere, within 12 to 15 feet from the ground." Further on they write: "As one proceeds toward the plateau of the Andes, those insects disappear and the air one breathes becomes pure . . . at a height of 200 toises (1500 feet) mosquitoes and zancudos are no longer feared."

I have observed two kinds of mosquitoes in Havana since December last, when I began to study those insects. One species is large, of a yellowish color, with thin, long legs, and without any particular markings; I suppose it must be the identical *zancudo* which worried Cortes' men on the sandy plains of San Juan de Ulua in 1519, and the same which La Sagra describes as the *Culex Cubensis*. The length of its body, measured from the root of the proboscis to the anal extremity, varies between 5 and 7 millimetres. This species comes out exclusively at night, generally between 9 and 10 o'clock, and pursues its annoying evolutions until daybreak. All the specimens which I have found inside of mosquito-nets (in the morning) have belonged to that species; and they remain part of the day in that position digesting the blood which they have sucked. The other species is the *Culex mosquito*, specimens of which were taken to Paris by the

distinguished Cuban Naturalist, Felipe Poey, in 1817 or 1820, and were there classified by M. Robineau Desvoidy under that name. I have noticed two varieties of this species: one large, with a slight, graceful figure, vigorous, of a dark gray color, somewhat smaller than the *C. Cubensis*; the other only measures from 4 to 4.5 millimetres. I have not sought for particular differential characters between these two varieties of the same species, their respective size sufficing for my present object.

The two species of mosquitoes to which I have referred do not come out at the same hours: the *zancudo* comes out at night and the *C. mosquito* in the daytime. This distribution of the day and night between the two species made me think that the *zancudo*, notwithstanding its larger size and more robust appearance, might not be constituted to stand the heat of our summer sunshine. I tried, therefore, the following experiment. On the 9th of June, at noon, I exposed to the direct rays of the sun the bulbs of my psychrometer; after half an hour the dry bulb marked 42° 0.25 C. and the wet bulb 3 L° 0.75. I then substituted in place of the instrument a tube in which a *zaneudo* had been confined for 5 days, but continued lively and agile; after 5 minutes' exposure the insect was dead. I then substituted another tube containing a *Culex mosquito*, and after leaving it exposed to the sun during 15 minutes it was still alive and continued to live another 24 hours in its tube.

It is well known that only the female mosquitoes bite and suck blood, while the males feed on vegetable juices, principally the sweet ones; but I have not found it mentioned in any author that even the females never bite before having been fertilized. This, at least, I infer from the following experiments.

A female *C. mosquito*, caught soon after breaking loose from its pupa-case, and kept alive during three days, cannot be got to bite during that space of time. I have several times repeated the experiment and always with a negative result.

Female mosquitoes which are caught pairing bite and suck blood readily very soon after they are parted.

Finally, those which are caught in the act of biting and sucking blood, will as a rule, lay eggs after a few days, while the fertilized females which have not been allowed to suck blood die without every laying any ova.

We are thus led to infer that the craving of the female mosquito for live blood is not meant to supply an indispensable article of food. Indeed it seems improbable that for the nourishment of so small a body, such a disproportionate quantity of rich blood be needed. I have come to the conclusion that the sucking of blood is intended for another object connected with the propagation of the species. The likeliest hypothesis seems to be that the feed of blood acts through the degree of heat which it procures. If, for instance, the maturation of the ovules contained in the ovaries of the mosquito demands a temperature of 37°C, the latter could scarcely be obtained by any other means so readily as by the insect filling itself with a fair amount of blood of that temperature; and sometimes it may be more convenient for the mosquito to bite a patient attacked with fever, whose blood at 39° or 40° may prove more efficacious in hastening the process of ovulation. It will thus be understood why large insects like the

zancudo are able to absorb with a single bite the amount of blood required for the maturation of all the 200 to 350 ova which they lay at one sitting, while the smaller species, like the *C. mosquito*, have to bite and fill themselves several times with blood before beginning to lay, and generally require several sittings before all their ova are laid.

The three successive operations: fertilization, sucking of blood and laying of eggs, constitute the most essential phases of the mosquito's existence. The first of these operations, as in most other insects, probably, need not occur more than once in order that the impregnated seminal sack of the female shall retain the faculty of fertilizing all the ova which may thereafter traverse its oviducts. In the Cuban bee, according to Felipe Poey, a single fecundation by the male, suffices for all the thousands of eggs which the female bee lays during the two or three years of its life. With the females of the various species of the genus *Culex*, which, till now, had been observed, there had been no occasion to test whether such a prolonged fertilizing faculty existed, inasmuch as all their ova were laid at a single sitting; but the case is different with the females of the *Culex mosquito*. These lay their ova separately or in files of 9 to 15 either isolated or in groups, sometimes upon the water or else upon solid bodies not too far removed from the level of the water, so that a moderate elevation of that level will allow the water to cover them. My explanation about the need of several bites and feeds of blood before the *C. mosquito* is able to lay all its ova, maybe purely hypothetical; it is nevertheless a fact that the females of that species are always ready to bite a second time after they have digested all the blood which had been sucked at a previous bite. A female *C. mosquito*, caught (in Havana) in January of the present year, had bitten 12 times and laid eggs three times in the course of the 31 days which it lived; its death having occurred in New York where it was exposed to temperature below the freezing point.

With the captive females of the *C. Cubensis* (*C. Pungens*), I have never been able to obtain a second bite, whether it had or had not laid its ova. Possibly, however, when at large they may need to bite several times before laying; for I have occasionally seen them come to bite my hand, with some blood already in their stomach. This I have attributed to a previous bite which had been interrupted before the insect had been able to draw its full allowance of blood.

Evidently, from the point of view which I am considering, the *Culex mosquito* is admirably adapted to convey from one person to another a disease which happens to be transmissible through the blood; since it has repeated opportunities of sucking blood from different sources, and also of infecting different persons; so that the probabilities that its bite may unite all the conditions required for the transmission will thereby be greatly increased. On the other hand, inasmuch as the *C. Cubensis* absorbs a larger quantity of the infectious blood at each feed, its mouth-parts may retain a larger amount of virus, and perhaps produce a graver inoculation when it happens to attack a non-immune a few moments after having bitten the patient, its first bite having been interrupted. In that case, a graver infection might result but the chances of its occurring would be much less.

The mosquito commences its operation of stinging by tentatively exploring the skin with the point of its proboscis until it finds a suitable spot. It then takes a firm position upon its six feet (sometimes the two hind legs are raised above its back), the thorax is strongly bent down while the head and the proboscis assume a vertical position. Next, with the naked eye or, better, with the assistance of a magnifying glass, the sheath is seen to bend backwards, at its upper part, gradually assuming the shape of an horizontal < the two branches of which gradually come closer together as the sting penetrates deeper into the skin. The sting is then seen as a very slender wire stretching between the extremities of the horizontal < figured by the sheath, and moving up and down in unison with the maxillary palps, until a blood capillary has been reached. The insect remains motionless while it fills itself, apparently without effort, with the red warm blood of its victim. During the bite a sharp, instantaneous, burning sensation is sometimes felt, owing to the saliva which the mosquito instills into the wound through the end of the sheath, the conical extremity of which remains caught between the edges of the wound. The insect's stomach becomes distended and the blood is seen through the transparent lateral walls of its body. Several minutes are generally required for the completion of the operation; as long as seven in some cases which I have timed.

It is a well-known fact that, while mosquitoes are never wholly absent from Havana, they are much more abundant at some seasons of the year. It appears to me that they increase in numbers from April or May till August, and thereafter gradually decrease till February or March. Another point, however, requires to be borne in mind, inasmuch as it affords an explanation of the recurrence, hitherto unaccounted for, of yellow fever epidemics without new importation, in localities previously considered as immune. I allude to the hibernation of mosquitoes, a phenomenon which is not observed in our climate, at least in all its phases; but which constitutes, according to the best authorities, the regular mode by which the species is propagated in cold climates, during winter. Taschenberg informs us that: "the fertilized females of the last generation hibernate during winter in out-of-the-way places such as the cellars of dwellings, and set about propagating their species the following spring."

Among the conditions which favor the development of mosquitoes may be mentioned; heat, moisture, the vicinity of stagnant waters, low, dark localities sheltered from the wind, and the summer season. It is necessary, however, to bear in mind Humboldt's observation that the abundance of mosquitoes is not always in accordance with recognizable meteorological or topographical conditions.

I have already referred to the difficulty which our mosquito, by reason of its comparatively small wings, must experience in its upward flight after it has filled itself with blood. It will also be hindered by the same cause, from going far from the place where it has accomplished its last bite, and, in general, from traveling any considerable distance through the air without resting. This circumstance will not prevent, however, its being conveyed, hidden among clothes, caught under a hat, inside of a traveling bag, etc., to considerable distances, after a recent bite, perhaps carrying upon its mouth parts the inoculable germ of the disease.

The preferences which mosquitoes show for certain races and

individuals should also be borne in mind; the African race being, apparently, the one least tormented by them, and the greatest sufferers being the Northern races newly arrived in the tropical regions of America. It is probable that this may be due to the comparative thickness of the skin, and to peculiarities in the cutaneous capillary circulation, since those circumstances must influence the facility with which the female mosquito will be able to procure itself the blood which it requires in order to accomplish its life cycle.

After this long, but necessary account of the habits of our Cuban mosquitoes, and of the *Culex* mosquito in particular, let us consider by what means that insect might transmit the yellow fever, if that disease happens to be really transmissible through the inoculation of blood. The first and most natural idea would be that the transmission might be effected through the virulent blood which the mosquito has sucked, amounting to 5 and even to 7 or 9 cubic mm, and which, if the insect happens to die before completing its digestion, would be in excellent condition to retain during a long time its infecting properties. It might also be supposed that the same blood which the mosquito discharges, as excrement, after having bitten a yellow fever patient, might be dissolved in the drinking water, whereby the infection might be conveyed if the latter were susceptible of penetrating by the mouth. But the experiments of Ffirth and other considerations arising from my personal ideas regarding the pathogenesis of yellow fever, forbid my taking into account either of those modes of propagation, as I shall now explain. When the U. S. Yellow Fever Commission took their leave, two years ago, they presented us with a valuable collection of microphotographs from preparations made by our corresponding Member, Dr. Sternberg, showing what, to me, appeared to be a most striking feature, namely, that the red blood-globules are discharged unbroken in the hemorrhages of yellow fever. This fact taken in connection with the circumstance that those hemorrhages are often unattended with any perceptible break in the blood vessels, while, on the other hand, they constitute a most essential clinical symptom of the disease, led me to infer that the principal lesion of yellow fever should be sought for in the vascular endothelium. The disease is transmissible, it attacks but once the same person, and always presents in its phenomena a regular order comparable with that observed in the eruptive fevers, all of which circumstances suggested to my mind the hypothesis that yellow fever should be considered as a sort of eruptive fever in which the seat of the eruption is the vascular endothelium. The first period would correspond to the initial fever, the remission to the eruptive period, and the third period would be that of desquamation. If the latter phase is accomplished under favorable conditions, the patient will only show evidence of an exaggerated transudation of some of the liquid elements of the blood through the new endothelium; if the conditions are unfavorable, a defective endothelium will have been produced, incapable of checking the figured elements of the blood: passive hemorrhages will occur and the patient may find himself in imminent danger. Finally, assimilating the disease to small-pox and to vaccination, it occurred to me that in order to inoculate yellow fever it would be necessary to pick out the inoculable material from within the blood vessels of a yellow-fever patient and to carry it likewise into the interior of a blood vessel of the person who was to be inoculated. All of which

conditions the mosquito satisfies most admirably through its bite, in a manner which it would be almost impossible for us to imitate, with the comparatively coarse instruments which the most skillful makers could produce.

Three conditions will, therefore, be necessary in order that yellow fever may be propagated: 1. The existence of a yellow fever patient into whose capillaries the mosquito is able to drive its sting and to impregnate it with the virulent particles, at an appropriate stage of the disease. 2. That the life of the mosquito be spared after its bite upon the patient until it has a chance of biting the person in whom the disease is to be reproduced. 3. The coincidence that some of the persons whom the same mosquito happens to bite thereafter shall be susceptible of contracting the disease.

The first of these conditions, since Dr. Ambrosio G. del Valle has been publishing his valuable mortuary tables, we may be sure, has never failed to be satisfied in Havana. With regard to the 2d and 3d, it is evident that the probabilities of their being satisfied will depend on the abundance of mosquitoes and on the number of susceptible persons present in the locality. I firmly believe that the three above mentioned conditions have, indeed, always coincided in years when yellow fever has made its greatest ravages.

Such is, Gentlemen, my theory; and I consider that it has been singularly strengthened by the numerous historical, geographical, ethnological and meteorological coincidences which occur between the data which I have collected regarding the mosquito and those which are recorded about the yellow fever; while, at the same time, we are enabled by it to account for circumstances which have until now been considered inexplicable under the prevailing theories. Yellow fever was unknown to the white race before the discovery of America, and, according to Humboldt, it is a traditional opinion in Vera Cruz that the disease has been prevailing there ever since the first Spanish explorers landed on its shores. There also, as we have seen, the Spaniards since their first landing have recorded the presence of mosquitoes; and with greater insistence than in any other place in America, in the identical sand-mounds of San Juan de Ulloa (the present site of Veracruz). The races which are most susceptible to yellow fever are also the ones who suffer most from the bites of mosquitoes. The meteorological conditions which are most favorable to the development of yellow fever are those which contribute to increase the number of mosquitoes; in proof of which I can cite several local epidemics regarding which competent authorities assert that the number of mosquitoes during the prevalence of yellow fever was much greater than on other occasions; indeed, it is stated in one instance that the mosquitoes were of a different kind from those which were usually observed in the locality, having gray rings around their bodies. Regarding the topography of the yellow fever, Humboldt points out the altitudes beyond which mosquitoes cease to appear, and in another passage gives the limits above the sea-level within which the yellow fever may be propagated. Finally, in the notorious case of the U. S. Steamship Plymouth, in which two cases of yellow fever occurred at sea, after the vessel had been disinfected and frozen during winter, four months after the last previous case had occurred on that vessel (the preceding November), the facts can be readily accounted for by the hibernation of mosquitoes which had bitten the former yellow fever

patients, and, which, upon finding themselves again within tropical temperatures, recovered from their lethargic condition and bit two of the new men of the crew.

Supported by the above reasons, I decided to submit my theory to an experimental test, and, after obtaining the necessary authorization, I proceeded in the following manner.

On the 30th of last June, I took to the Quinta de Garcini a mosquito which had been caught before being allowed to sting, and there made it bite and fill itself with blood from the arm of a patient, Camilo Anca, who was in the fifth day of a well characterized attack of yellow fever of which he died two days later. I then picked out F. B., one of twenty healthy non-immunes who have continued until now under my observation, and made the same mosquito bite him. Bearing in mind that the incubation of yellow fever, in cases which allow its limits to be reckoned, varies between one and fifteen days, I ordered the man to be kept under observation. On the 9th of July, F. B. began to feel out of sorts, and on the 14th he was admitted to the Military Hospital with a mild attack of yellow fever perfectly characterized by the usual yellowness, and albumin in the urine which persisted from the third till the ninth day.

On the 16th of July, I applied a mosquito at the same Quinta de Garcini, to a patient, Domingo Rodriguez, in the third or fourth day of yellow fever; on the 20th, I allowed the same mosquito to bite me and, finally, on the 22nd I made it bite A. L. C., another of the 20 men who are under observation. Five days later, this man was admitted at the Hospital with fever, severe headache, pain in the loins and injected eyes; these symptoms lasted three days, after which the patient became convalescent without having presented any yellowness nor albuminuria. His case was, however, diagnosed as "abortive yellow fever" by the physician in charge.

The 29th of July, I made a mosquito bite D. L. R. who was going through a severe attack of yellow fever at Quinta de Garcini, being then in its third day. On the 31st, I made the same mosquito bite D. L. F., another of my 20 men under observation.

On the 5th of August, at 2 a.m., he was attacked with symptoms of mild yellow fever; he subsequently showed some yellowness but I do not think that he developed any albuminuria; his case was, nevertheless, diagnosed "abortive yellow fever."

Finally, on the 31st of July, I applied another mosquito to the same patient, D. L. R. at Quinta Garcini, his attack having then reached its fifth day and proving fatal on the following one. On the 2d of August I applied this mosquito to D. G. B., another of my twenty non-immunes. Till the present date (12th) this last inoculation has not given any result; but, as only 12 days have elapsed, the case is still within the limits of incubation.

I have to state that the persons mentioned above are the only ones who were inoculated with mosquitoes, in the manner described; and that since June 12th, till now (in the course of seven weeks), barring my first three inoculated men, no other case of confirmed or abortive yellow fever has occurred among the twenty non-immunes, whom I have had under observation.

These experiments are certainly favorable to my theory, but I do not wish to exaggerate their value in considering them final, although the accumulation of probabilities in my favor is now very remarkable. I understand but too well that nothing less than an absolutely incontrovertible demonstration will be required before the generality of my colleagues accept a theory so entirely at variance with the ideas which have until now prevailed about yellow fever. In the mean time, I beg leave to resume in the following conclusions the most essential points which I have endeavored to demonstrate.

Conclusions

(1) It has been proved that the *C. mosquito*, as a rule, bites several times in the course of its existence, not only when its bite has been accidentally interrupted, but even when it has been allowed to completely satisfy its appetite; in which case two or more days intervene between its successive bites.

(2) Inasmuch as the mouth-parts of the mosquito are very well adapted to retain particles that may be in suspension in the liquids absorbed by that insect, it cannot be denied that there is a possibility that said mosquito should retain upon the setae of its sting some of the virulent particles contained in a diseased blood, and may inoculate them to the persons whom it afterwards chances to bite.

(3) The direct experiments undertaken to decide whether the mosquito is able to transmit yellow fever in the above stated manner, have been limited to five attempted inoculations, with a single bite, and they have given the following results: One case of mild yellow fever, perfectly characterized, with albuminuria and icterus; two cases diagnosed as "abortive yellow fever" by the physicians in charge; and two ephemeral fevers without any definite characters. From which results it must be inferred that the inoculation with a single bite is insufficient to produce the severe forms of yellow fever, and that a final decision as to the efficacy of such inoculations must be deferred until opportunity is found for experimenting under absolutely decisive conditions, outside of the epidemic zone.

(4) Should it be finally proven that the mosquito inoculation not only reproduces the yellow fever, but that it constitutes the regular process through which the disease is propagated, the conditions of existence and of development for that dipterous insect would account for the anomalies hitherto observed in the propagation of yellow fever, and while we might, on the one hand, have the means of preventing the disease from spreading, non-immunes might at the same time be protected through a mild inoculation.

My only desire is that my observations be recorded, and that the correctness of my ideas be tested through direct experiments. I do not mean by this that I would shun the discussion of my opinions; far from it, I shall be very glad to hear any remarks or objections which my distinguished colleagues may be inclined to express.

Biography of Dr. Henry Rose Carter

In 1904, Henry Rose Carter and Carlos Finlay were nominated for the Nobel Prize in Medicine by Sir Ronald Ross, who in 1898 had shown that malaria was transmitted by mosquitoes. Ross nominated them for their work that led to proving the *Aedes aegypti* mosquito was the vector for yellow fever.

Carlos Finlay had provided the theory that mosquitoes carried the agent of yellow fever, but for 20 years he was unable to transmit a single case. Carter added the key epidemiological evidence that demonstrated how an insect could serve as the intermediate host. His observations explained Finlay's failures and most likely convinced Walter Reed and the Yellow Fever Board to seriously consider mosquito transmission.

Henry Rose Carter was born at Clinton Plantation, Caroline County, Virginia, on August 25, 1852 and attended Aspen Hill Academy. He enrolled in the University of Virginia as an engineering student. A leg injury around the time of his graduation made him reconsider the arduous life of an engineer for the more sedate one of a physician and he enrolled in the University of Maryland School of Medicine. He joined the Marine Hospital Corps (forerunner of the Public Health Service) in 1879.

For the next 20 years, he served along the Gulf Coast of Louisiana where he observed the strange but uniform timing of yellow fever outbreaks on ships traveling from Central and South America. He noted that within a day of leaving port, yellow fever cases may occur but then it was 2 weeks before the next set of cases appeared.

In 1898, he was called to the two small towns of Orwood and Taylor, Mississippi to investigate a yellow fever outbreak. There he put his observations to the test, meticulously documenting exposure to cases and recording the timing of every case.

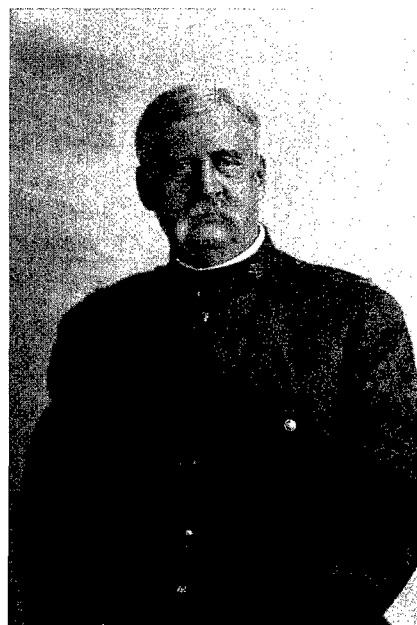
Based on his observations and analysis he concluded that the infectious agent "leaving the patient must undergo some change in the environment before it is capable of infecting another man." He thought this period took about 2 weeks, and he called it the period of "extrinsic incubation."

The Yellow Fever Board had the good fortune of Carter's assignment to Havana in 1899 as Chief Quarantine Officer for the Marine Hospital Service. In 1900 as the Board developed their

plan for studying the etiology of yellow fever, they were able to keep in close touch with Carter and thus benefit from his experience.

Dr. Carter served as director of hospitals in the Panama Canal Zone from 1904 to 1909. In 1915 he was commissioned Assistant Surgeon General of the Public Health Service by a special act of Congress. By this time his professional interests had expanded to include malaria. He worked with the Rockefeller Foundation, was a special advisor to the Peruvian government, and served as a member of various health boards.

Carter died in Washington, DC, on September 14, 1925. In an obituary that appeared in the *Journal of the American Medical Association* in September 1925, Dr. Carter was called "a clear analyst and a practical thinker."



Historical Background: Published in the *New Orleans Medical and Surgical Journal*, May 1900, Volume 52, pages 617-636, this article describes observations on the occurrence of yellow fever in two rural Mississippi towns, Orwood and Taylor. Dr. Henry Rose Carter of the U.S. Marine Hospital Service and his assistant, Dr. Harry Gant, meticulously tracked and recorded the time intervals between cases occurring in these two small communities. Carter had been making observations on yellow fever for many years, and in the article he explains why these two small communities were so ideal for this study. These new observations led him to two conclusions. First, a place could not be infected and second, that the material causing the disease had to undergo some change in the environment. He called this the period of "extrinsic incubation." It was this second finding that helped convince the Yellow Fever Board to pursue the mosquito theory. It also provided a key piece of information on the time interval needed for an infected mosquito to incubate the yellow fever virus before it was transmissible. The paper has been edited for space and readability. An ellipsis (. . .) indicates where text has been deleted from the article.

A Note on the Interval between Infecting and Secondary Cases of Yellow Fever from the Records of the Yellow Fever at Orwood and Taylor, Mississippi in 1898

H. R. Carter, MD, United States Marine Hospital Service

When a man develops yellow fever in an uninfected place, if the conditions of his environment and of the people therein are favorable, some of the people will develop, the disease (see foot note No. 1.).

A proper inquiry is of the *space of time* which intervenes between the development of the first case which infected the environment and the development of the cases contracted from this environment; and it is to give some data on this subject, observed at Orwood and Taylor, Miss., in 1898, that this note is presented.

The question set by the writer is, *how long in time in every particular instance determinable at Orwood was it between the development of a case of yellow fever in an uninfected place and the development of the next case (and other cases) contracted (indirectly) from the infection from the first case?*

There are quite a number of observations in various reports and histories of epidemics of isolated instances bearing on this subject, but no great number are so observed and so recorded as to be beyond question reliable. Indeed, it is obvious that the conditions for reliable observation on this matter are not common. It is necessary:

(1) That the date be known of the development of the case of yellow fever which caused the infection of the environment, i. e., of the "infecting case."

(2) That it be *known* that the cases accounted as contracted from the environment in question *were so contracted in fact*, i. e., were not contracted from other sources, including fomites brought by the first sick man.

(3) That the exposure of these secondary cases be known to be practically continuous from the development of the first case.

Now yellow fever is essentially a disease of towns, and it is easy to see how rarely are we able to fulfil the first two conditions in a town of any size. If we *are* able to determine the first case near enough to its development to watch for the secondary cases (which does not always occur), we do not usually get more than one observation, i. e., of the people contracting the fever in the

house with the patient, the intercommunication of people in a town being such that after this it is difficult to certainly trace the source of infection of persons developing the fever.

Another difficulty is that observations are not usually made or records kept of a kind to determine the problem we are investigating, so that if the conditions are favorable for observation, the records do not properly preserve them.

The epidemic of yellow fever at Orwood, Miss., in 1898, was peculiarly well suited for observing this element in the propagation of yellow fever, and the record of it, which, by the courtesy of Drs. Gant and Mathews, of the Mississippi State Board of Health, I am permitted to use, was kept with particular reference to throwing light on this subject, as well as some others involved in it.

Orwood is not a town, or even a hamlet. It is a "Neighborhood." An agricultural community about *twelve miles* from the railroad at Taylor, consisting almost exclusively of white people, living on their farms, seldom closer than a mile apart, working their own lands with little hiring, having little intercourse with the outside world, practically all non-immune to yellow fever; intelligent, law-abiding and well disposed. People who were at once intelligent enough to know, and honest enough to tell, the truth and to co-operate in good faith with the efforts made to trace the infection of each case and by stopping visiting, etc., to limit the spread of infection already introduced. This was rendered the easier, because Dr. Gant, who made the diagnosis of yellow fever, and under whom (directly or indirectly) all sanitary measures were conducted, was much beloved in the community, and had their entire confidence. The diagnosis of yellow fever was not disputed, although there were no deaths in Orwood until several weeks afterwards, and very few in all. A greater tribute to the good faith of the community, or to its confidence in Dr. Gant, can scarcely be given.

Yellow fever was introduced as follows

(1) On August 6 by Miss Gray, four days from her uncle's house at Taylor, then infected, to "Gray Mansion." Miss Gray

had been at Taylor four days and states that she brought no clothing with her save what she was wearing and one night wrapper.

(2) Ed. Gray, uncle to above, brought to the same house on August 25, from the same house at Taylor, where he had developed yellow fever four days before. Brought clothing in trunk, not open or unpacked up to September 3 (date of my first visit).

(3) Mrs. Gray, grandmother of Miss Gray, sickened en route from same house at Taylor to same house in Orwood, "Gray Mansion." Also on August 25 brought clothing with her, opened trunk day after arrival. All of these were sick in the "Gray Mansion."

(4) Mrs. Gray, daughter-in-law of Mrs. Gray, developed yellow fever en route from same house at Taylor to her house in Orwood neighborhood, on August 25, also. Her house was not the "Gray Mansion," but some miles from it. Brought furniture, bedding, etc., with her. Taylor is about twelve miles from Orwood, over a bad road, and normally there is not much communication between the places, mainly among the Grays.

We thus have yellow fever introduced from the outside into two houses in Orwood on August 6 and August 25. Almost certainly fomites were introduced (at both houses) on the 25th and possibly on the 6th; although the history, especially the subsequent history, seems to negative this.

The "Gray Mansion" was the point of spread. This house was infected prior to the arrival of Ed. Gray and Mrs. Gray in it, as is shown by the occurrence of four or five other cases there *before* their arrival. Prior to their arrival people had been visiting at the Gray Mansion. They, the Grays, were prominent people and popular in the community. After the 25th a much larger number of people came to nurse and sit up with old Mrs. Gray and Ed. Gray and the other sick. This house was virulently infected with yellow fever of mild grade. Of forty-six people non-immune to yellow fever, who were in this house on or after the 21st of August, forty-five developed yellow fever, very few having any other exposure.

The latter part of August, the 30th, I think, the diagnosis of yellow fever was made by Dr. Gant at the Gray house and elsewhere in the community and at Taylor as well, and visiting, save such as was necessary to care for the sick (the physicians directing this), was ordered stopped and was stopped.

We thus had at Orwood

(1) An intelligent, well-disposed community.

(2) Living almost entirely to itself in isolated farm houses, separated far beyond the aerial conveyance of yellow fever, and with very few negro houses, or other living houses on the same farm.

(3) A definite introduction of the disease.

(4) An early diagnosis, there being then but one focus active in spreading fever from which many people had contracted it to develop it later.

(5) The cessation of visiting after the announcement of the fever, except such visiting as was known to the reporter.

(6) The almost entire absence of negroes in the community, and that none of them had so far developed the disease. Infection among negroes is confessedly difficult to trace.

Obviously it presented an ideal field for the study of "house infection" and properly studied should throw light on several problems connected with this disease, among them the subject we have mentioned.

To avail ourselves of the best advantage of the situation for this purpose it was agreed at the instance of the writer to keep the records by "houses" and to scrutinize carefully the probable and possible exposures to infection of those developing yellow fever even after this knowledge ceased to be of any importance from a sanitary (preventive) standpoint.

With this preliminary let us examine the "house record" of Orwood. This was kept by Dr. Mathews under the auspices of Dr. Gant, much of the data being furnished by Dr. Gant. It has been compared with some notes (of the earlier cases) of my own and some of later cases, by Dr. von Ezzdorf (U. S. M. H. S.), with which in this matter it agrees. Much pains has been taken to exclude doubtful statements, or to indicate that they are doubtful. I cannot give the full weight to records of houses in which the cases appear late in the epidemic, as the source of infection is less certainly traced after many foci of infection are developed and the isolation has continued until it is irksome. Only those in the early part of the epidemic then will be relied on.

For the purpose of this paper, the records used as reliable are believed to be so (see foot note No. 3).

House 1. — Gray House-Orwood

Sallie Wilson Gray, at Dr. Gray's, in Taylor, July 29 to August 2, at 6 p.m., developed fever, August 6, 11 p.m.; Lucille Gray, room mate of above, August 23, 11 a.m.; Annie Gray, August 24, 11 a.m.; Sam Gray, August 24, 7 p.m.; Pate Gray, August 25, 2 a.m.; Cecil Gray, August 25, 12 midnight; Christobel Gray, August 25, 7 p.m.; Ed. Gray brought home from Taylor (sick August 21) on August 25; Mrs. Charles Gray, brought home from Taylor, sickened en route, August 25; Mrs. Knox, nurse, arrived August 23, 1 a.m., sickened August 31, 2 a.m.; Mrs. McCarter, nurse, arrived August 27, 2 p.m., sickened September 1, 9 a.m.

Dr. Mathews also developed fever here five days from first exposure (four days' continuous exposure), but was not treated here.

Several others, nurses and helpers, also developed fever in this house, some being treated here and some taken elsewhere. All who lived in the house developed fever there and all save one who entered it after August 21.

Here there were sixteen and one-half days between the first case and the second and five others within the next two and one-half days.

All of the above to Edward Gray were continuous residents, of this house from and before August 6.

Miss Gray denied that she brought any clothing or fabrics or anything whatever from Taylor, save the clothing she was then wearing on her person. Even had she done so we would scarcely accuse any such apparel, brought already infected from Taylor, as the probable cause of this outbreak. We would have expected her sister (and room mate) to have developed fever long before the boys, and certainly prior to the twenty-first day of the introduction of the already infected fomites. I think; then, there is little reason to ascribe the infection of these people to fomites brought infected from Taylor. Still, although improbable, this is possible, and if any one wishes on this account to exclude this case from the "infection of environment by the patient" he can do so. The fact remains that it was sixteen and one-half days between the development of the first and second cases (see foot note No. 5).

[House No. 2.—House No.17. are similarly described.]

House 18. — I. B. Orr

Langdon Orr, young man, sick August 22, 3 p.m., at Gray House on evening of August 18; Miss Maggie Orr, at Gray House, August 24 and 27, sickened August 30, 1 a.m.; Dr. Mathews brought in sick from Gray House September 3, in afternoon; I. B. Orr continuously exposed at Dr. Gray's house from August 25, sickened September 6; Miss Carrie Orr at Gray's August 25 and all night of 27, sickened September 7; James Orr, September 20; Harry Orr, September 24; Miss Bell Orr, September 27; Mrs. I.B. Orr, October 7; Lessie Orr, October 7; Miss Mary Ann Orr, October 7.

Miss Mary Orr was at the Gray House in August, and once in early September, and is the only person who visited that place after August 20, who did not develop yellow fever under such conditions that must (most probably) be ascribed to the infection of the house. This is an extremely interesting house and my own notes on it up to and including September 4 are full. The house is a large, airy one. The family consisted of ten. They were close friends and relative of the Grays at Orwood, and visited there although it was some miles distant. Mr. Orr and some one of the elder daughters (Maggie, Carrie and Mary) were there almost every day from the 25th on, nursing the sick, etc. Mrs. Orr, having many household cares, and the younger children did not go. The whole family had fever. Visiting stopped when Mr. I. B. sickened, there being then four sick with fever in the house, and all who could help were needed at home. Whether Maggie Orr, Mr. Orr and Carrie Orr contracted fever from Gray's or from their own environment infected by Langdon Orr, maybe a question. The writer believes that enough is known to decide in the case of the first, but it is not the purpose of this paper to use cases as secondary which may have contracted the disease elsewhere, or vice versa. It will be discussed later on.

An interval between the infecting case and the first case contracted from the infected environment cannot be determined for this house.

[House No. 19. and House No.20. are similarly described.]

Taylor, Mississippi

Records of the same kind, by houses, were made of the cases at Taylor, but the conditions were far less favorable.

(1) The place was almost a hamlet, some of the houses being close enough for aerial transmission of infection between them, with a common loafing place in the railroad depot and the store. The depot was infected early; whether the store was we did not determine.

(2) The fever existed quite a while, six weeks at least, before it was diagnosed, and several (four or five) foci of infection had been formed, and nearly or quite a dozen cases had occurred.

(3) There was a considerable negro population, thickly settled, and mixed with the whites, of whose visiting and conveyance of fomites no one can predicate. The presence of this race introduces an element of uncertainty in tracing the propagation of yellow fever that it is difficult to overestimate.

(4) Some of the notes taken at Taylor were necessarily taken some time after the occurrences to which they refer, and thus there is question about dates and (I think) sometimes of diagnosis. There are a few houses at Taylor of which the records are

definite and correct; the date being either the date of record (by Dr. Haralson or myself) or so fixed by record (of deaths, etc.) that they can be relied on. I give them:

House of Rev. Mr. Williams

Twelve in family. House very clean and well kept. Isolated from others. Two colored servants.

Hampton, August 7, at night, eldest son; believed to have been exposed at Dr. Gray's. Died, with suppression and black vomit, turning very yellow, August 10. Both this death and Dr. Gray's were ascribed to "Congestion"; Grover (age 12), August 27, at night; Mrs. Williams, September 3, 8 a.m.; Ora (24), September 4, 12 night; Lee (22), September 6, 9 a. m., Mark (9), September 8, at night; Sidney (17), September 9, 9 a.m.; Viva (3½), September 9, 10 a.m.; Susan Thomas (colored), September 9, during the night; Cleveland (6), September 10, at night; Nettie (26), September 15, 4 p.m.; Charles (15), September 19, 11 a.m., Mr. Williams, September 23, 4 to 5 a.m., Laura Spicer (col.) September 23.

Twenty days is the interval here between the first (infecting) and secondary cases. The secondary cases, thirteen in all, followed in fairly rapid succession after they began. The children were kept out of the house as much as possible, and slept upstairs as far as possible from the sick rooms (until the latter became too numerous to be avoided) for the purpose (and we believed with the result) of delaying some of the attacks, so that all might not get sick at once. An explosion—several cases in one day—is not an uncommon occurrence in large households.

[The Sisk Houses and Taylor Hotel are similarly described.]

Grouping the results obtained, we have the following summary [Table II]:

The "intervals" for the twelve houses run fairly uniformly mainly from 2 to 3 weeks, one house giving less than two weeks (11½ days) and two houses more than three—21½ and 23 days respectively.

The temptation to quote instances observed elsewhere; to collate them with the result given above and to attempt to formulate the usual inferior limit (see foot note No. 8), for the time between the infecting and secondary cases is considerable, but this note was intended to give the interval of time which *did* elapse in all the houses at Orwood and Taylor between the first case of yellow fever and those believed with reasonable certainty to have developed yellow fever from infection brought to the house by the first case.

This ends our note, but it is judged best to give an appendix of the records of all the houses in Orwood (although some give no determinative information on this subject). The reader can judge for himself whether there was any improper selection of houses; if any were omitted which should have been taken in the foregoing table or taken which should have been omitted. For Taylor this is not possible, some of the data being not only indeterminate but unreliable. Those given for Taylor are all of which the writer has satisfactory record and which he believes to fulfil the required conditions.

Foot Notes

No. 1

It is assumed that the infection of yellow fever may be conveyed directly from one sick of that disease to his environment,

TABLE I
SUMMARY FOR ORWOOD AND TAYLOR

House	Infecting Case	First Secondary Case	Interval in Days	Secondary Case		People in House	Remarks
				Number	Days		
Orwood 1	Aug. 6	Aug. 23	16 ½	6	2 ½	(*) 7	[Of 46 person exposed, 45 probably contracted fever here.
2	Aug. 29	Sept. 13	15	3	1	(*) 4	
3	Aug. 29	Sept. 13	20	4	5	(*) 5	
6	Aug. 31 or Sept. 1	Sept. 20	19 ½	5	7	7	3 secondary cases occurred in 1 (the first) day.
7	Sept. 3	Sept. 26	23	6	10	(?)	
9	Aug. 31	Sept. 22	21	4 or 5	13 or 28	6	Source of infection in last case doubtful.
10	Sept. 4	Sept. 20	16	2	2	(?)	Shorted interval of the list.
15	Sept. 2	Sept. 22	20 ½	1	...	(?)	
Taylor 16	Aug. 29	Sept. 9	11 ½	1	...	3	
	Aug. 30						
1	Aug. 7	Aug. 27	20	13	27	14	Secondary case developed in 14 days.
2	Aug. 17	Sept. 2	16	8 or 9	15	10	Paul Sisk is not rated as contracting fever at Jesse Sisks.
3	Aug. 10	Aug. 25	15 or 18	3 or 2	11 or 8	5	
	Aug. 11	Aug. 28					

*All continuously resident.

it being so generally admitted that it seems a waste of time to argue it; but the data recorded in this paper do not depend on or involve this theory or indeed any theory. They are simply facts that were observed.

[No. 2 — deleted.]

No. 3

Far more important than to determine the time between infecting case and secondary cases (or the inferior limit of this time) is to determine the limits of the period of incubation of yellow fever in one contracting it and the period of "house infection" or so-called extrinsic incubation (which of course are involved in the problem set ourselves). It will be recognized that the conditions at Orwood, and to a less degree at Taylor, were extremely well suited for the study of the former problems, and indeed the observations there are for this purpose extremely valuable; but as the writer has been collecting data on this subject since 1887, it seems better to collate these (Orwood and Taylor) observations with the others when time and convenience permit the work receiving the care it deserves.

[No. 4 — deleted.]

No. 5

When the source of infection of a household is fomites, we generally observe several cases developing about the same time, without the long interval between the first and other cases. Of course, the times of exposure to the fomites of different members of the household and individual susceptibility may be such as to make any variation in the dates of development. The statement, however, is *generally* true.

[No. 6 and No. 7 — deleted.]

No. 8

Obviously only the inferior limit is in question. A place may be infected and a person live in it an indefinite time without contracting yellow fever, the time depending on individual susceptibility (temporary or permanent) and other causes.

Individual susceptibility is a factor as well in determining the time of development of the first secondary case, and thus in determining our "interval." But where there are many who develop yellow fever in a house (as at Gray's and Williams') its influence is lessened. It is not reasonable to suppose the individual susceptibility of every one of a considerable number of people, developing yellow fever, to be less (or much less) than the normal.

[APPENDIX I. — deleted.]

APPENDIX II.

House No. 18, Orwood. We propose to further discuss the propagation of yellow fever at house No. 18, Mrs. Orr's:

Note that all those who sickened before September 20, had been exposed at the Gray House, a badly infected place; that none of those who had not been there exposed (at the Gray House), sickness prior to September 20.

Note also the considerable interval, thirteen days, between the development of the last case exposed at the Gray House and the first case not so exposed, and that the intervals between the cases known to be contracted from infection at Orr's house is much less.

From this alone I think we would be justified in saying that it is most probable that the cases arising prior to the 20th were contracted at the Gray House, and those from that date at Orr's. Orr's house being infected by some of the preceding cases.

If, in addition to this, we compare this house with all the others we have recorded, we find that none of them show so short a time as seven and a half days between the infecting and secondary cases, and unless Maggie Orr's case was to that except exceptional, it was not a secondary case, and therefore not contracted from infection of this residence by Langdon Orr.

The same cannot be said of the next two cases, 15 and 16 days respectively from the first. There are intervals which we have observed. The intervals of development September 6, 7, 20, 24 and 27 of the whole group do not correspond with what we have seen of secondary cases in other Orwood houses. While the group from the 20th on does so correspond.

The conclusion the writer would reach is that Miss Maggie Orr contracted her fever at Gray's; that it is highly probable that Mr. Orr and Miss Carrie Orr did also, and that only the cases from the 20th on were contracted from the infection of Orr's house; infected by some (it need not have been Langdon) of those who were sick in it.

APPENDIX III.

Obiter Dictum. — Broadly the question to be considered, and to which the data in the preceding paper may be contributory is this: *Is the time between the development of the case which infects its environment and the next other areas contracted therefrom (i.e., from the environment) usually so definite that a general statement of the limits of this time can be made?*

So far as the writer knows this (general) subject is not discussed in any systematic treatise on yellow fever, yet it is alluded to in several brochures and is now recognized (at least in a general working hypothesis) by many who have observed the spread of yellow fever in places where it is not endemic.¹

The time from the infecting to a secondary case obviously consists of three periods:

(1) The time from the development of the infecting case to the time the environment is capable of developing infection in other men, plus

(2) Time the individual in question is exposed to the environment before he contracts the disease, plus

(3) Time from the date of contracting the disease to its development in him.

In the general case all three are variants and, while this "time" includes all three, by itself it would give us little chance of

determining any one of them. It may, however, be made a factor in that determination if we have other data.

It is exceedingly desirable from a practical standpoint to determine the limits of the "period of incubation" of yellow fever and it was on this subject that the writer was engaged (since 1887), when he was impressed with the general uniformity of the interval between first and secondary cases in a number (5) of instances. Inquiry of more experienced observers showed that the phenomenon had been observed by others, and while further observation and inquiry showed that the uniformity first observed (16 to 18 days) was accidental and closer than generally found, yet there is much evidence to show that is usually "in the third week" (Jno. Wall of Tampa), or better, "usually *not prior to the third week*" that secondary cases develop.

It is the belief that the secondary cases follow immediately on the infecting case that causes the laity to doubt (generally to deny) the diagnosis of yellow fever, "because it has been ten days and no case has developed among the family."

The sanitarian cannot take this comfort to his soul (it would be a comfort to him were he the discredited diagnostician himself), or that which springs from the hope that the case did not infect its surroundings until a much longer time has elapsed. There is, of course, no definite limit of time at which we would call the situation "safe," or "unsafe," but hope of safety increases with the passage of the third week, and as the time beyond this passes.

This law (one will admit it at least as a working hypothesis) is also of value in predicting the progress of an epidemic which will spread. From the first (infecting) case to the first group of cases, infected at his house, is generally from two to three weeks. These form new foci (the original one remaining active), and in from two to three weeks more the second group of cases appears. At this time, four to six weeks, the fever should be "scattered" in tertiary foci, just beginning. Prior to this it is found *only in those who have had a common exposure*, seldom then in more than four to eight places, although it is not the number, but the common exposure, that is in question.

[Note]

1. Maximillian Corre, who does not believe that a man sick of yellow fever can infect his environment, *regarding the disease as a toxemia, not an infection*, probably has something on this subject, as there is an allusion to a subject involved in the "Extrinsic Incubation" of yellow fever in one of his lesser works. The writer been unable to see the work alluded to (also one of Corre's) and at present has access only to his own notes.

Biography of Dr. George Miller Sternberg

George Miller Sternberg was appointed as Surgeon General of the U.S. Army in 1893. Earlier that year his 900-page *Manuel of Bacteriology* had been published, establishing him as America's leading bacteriologist. He had, however, not come to this position through the life of an academic.

He was born at Hatwick Seminary, New York, on June 8, 1838, where his father was on the faculty. He was educated at the seminary and received his medical degree from the College of Physicians and Surgeons in New York City in 1860. He joined the Army in the early days of the Civil War and like many volunteers, he expected a short war followed by a return to the private practice of medicine. He served throughout the 4 years of Civil War, receiving official commendation for courageous services at the battles of Gaines' Hill, Turkey Bridge, and Malvern Hill. During the war he was captured and held briefly but escaped and evaded recapture, making his way back to Washington, DC. Later he suffered from an attack of typhoid. He remained in the service after the war, serving at frontier Army posts and participating in the Nez Percés Indian campaign. He also served at many different locations in the east.

Despite his rise through the ranks to become surgeon general, he was, however, first and foremost a scientist. A review of his bibliography, as compiled by the Surgeon General's office and published in *George M. Sternberg: A Biography* (Martha L. Sternberg, American Medical Association, 1920), reveals that the bulk of his career was devoted to chasing the cause of yellow fever. He wrote extensively on the epidemiology of the disease and on the theories of its etiology. He himself made no significant breakthroughs, but he did investigate and test the discoveries of others.

His first medical paper, *An Inquiry into the Modus Operandi of the Yellow Fever Poison*, published in the *New Orleans Medical and Surgical Journal* (July 1875), established him as the Army's leading expert on yellow fever. Of 155 publications and presentations, 43 (28%) were clearly about yellow fever. The others addressed general bacteriology, 38 (25%); disinfection 17 (11%); and malaria, 8 (5%). His pursuit of yellow fever spanned over 25 years. He battled epidemics in New York City, New Orleans, and Fort Barrancas, Florida where he contracted a near-fatal case. Survival meant he had lifetime immunity to the disease and could study it without fear of again becoming ill.

In 1879, yellow fever was epidemic in the U.S., and Sternberg was called to assist. In response to the outbreak, the Havana Yellow Fever Commission of the National Board of Health was established with Sternberg as secretary. Although the Commission failed to identify the cause of the disease or produce an effective control strategy, Sternberg added to his reputation as a leading expert in yellow fever and bacteriology. Throughout the 1880s his work in the areas of disinfection and bacteriology continued, and his reputation grew.

One of his first acts as Surgeon General in 1893 was to establish the Army Medical School in Washington, DC. He



accomplished this without funding by re-assigning talented officers to other designated positions in Washington and giving them additional duties to teach at his new school. Walter Reed was one of the officers so assigned. Over the years, Reed demonstrated his abilities and became a trusted associate. He was assigned by Sternberg to many varied and important duties, including heading the U.S. Army Typhoid Board that studied the terrible epidemics and deaths that ravaged camps of army volunteers during and after the Spanish-American War.

In 1900, it was clear that yellow fever was going to be a significant problem for the U.S. Army troops occupying Cuba, and Sternberg appointed the U.S. Army Yellow Fever Board to "study the diseases prevalent" on the island. This was one of several research boards he appointed while Surgeon General to work in the U.S., Cuba, Puerto Rico, and the Philippines.

After 10 years as Surgeon General, he retired from the Army in 1902. He then led two companies that sought to tear down the barely habitable slums of Washington, DC and build decent housing for the city's working poor. He died in Washington, DC, on November 13, 1915.

Historical Background: The following documents established the Yellow Fever Board and named its members. The memorandum from Surgeon General Sternberg to the Adjutant General of the Army (Fig. 1) requested the order that was issued as part of Special Orders No. 122 on May 24, 1900 (Fig. 2). The Surgeon General's request for orders specifically mentioned yellow fever, but for some reason the order when issued did not. Strangely William Bean in his book *Walter Reed — A Biography*, states that Sternberg was ambiguous about his desire for the Board to investigate yellow fever (p.109-110). The request for orders of May 23, 1900 and his follow-up letter to Reed (Fig. 3), completed several days later, clearly demonstrate that Sternberg wanted the Board to study yellow fever. Sternberg knew Reed very well and clearly trusted his abilities. He also knew that Reed and James Carroll had already done work on Sanarelli's claim that he had discovered the causative agent of yellow fever, the *Bacillus icteriodes*. Their work published in the *Medical News*, April 29, 1899 expressed their opinion that the *Bacillus icteriodes* was a strain of the hog-cholera bacillus. (The original documents reside in Record Group 112, National Archives and Records Administration.)

Memorandum, The Surgeon General to The Adjutant General May 23, 1900

OFFICE OF SURGEON GENERAL

Communications on official business should be addressed: "To the Surgeon General, U. S. Army, Washington, D. C."

71980 S

WAR DEPARTMENT

In reply refer to No.

WAR DEPARTMENT,

Surgeon General's Office,

Washington, May 23, 1900.

To the

ADJUTANT GENERAL OF THE ARMY.

Sir:

I have the honor to recommend that Major Walter Reed, Surgeon, U.S.Army, and Contract Surgeon James Carroll, U.S.Army, be ordered to proceed from this city to Camp Columbia, Cuba, reporting their arrival and instructions to the commanding officer of the post, the commanding general, Department of Havana and Pinar del Rio and the commanding general Division of Cuba.

I also recommend the organization of a medical board with headquarters at Camp Columbia, for the purpose of pursuing scientific investigations with reference to the infectious diseases prevalent on the island of Cuba and especially of yellow fever.

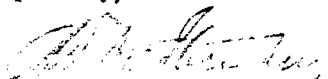
The board to be constituted as follows:-

Major Walter Reed; Surgeon, U.S.Army; Contract Surgeon James Carroll, U.S.Army; Contract Surgeon Aristides Agramonte, U.S.Army; and Contract Surgeon Jesse W. Lazear, U.S.Army.

Contract Surgeon Agramonte, is now on duty in the City of Havana and Contract Surgeon Lazear at Camp Columbia. It is not considered necessary to relieve them from the duties to which they are at present assigned.

The board should act under general instructions which will be communicated to Major Reed by the Surgeon General of the Army.

Very respectfully,



Surgeon General, U.S.Army.

Special Order No. 122, Department of the Army, Washington, D.C.
May 24, 1900

Special Orders }
No. 122 }

HEADQUARTERS OF THE ARMY,
ADJUTANT GENERAL'S OFFICE,
WASHINGTON, May 24, 1900

Extract

34. By direction of the Secretary of War, a board of medical officers is appointed to meet at Camp Columbia, Quemados, Cuba, for the purpose of pursuing scientific investigations with reference to the infectious diseases prevalent on the Island of Cuba. Detail for the board:

Major Walter Reed, surgeon, U. S. Army;

Acting Assistant Surgeon James Carroll, U. S. Army;

Acting Assistant Surgeon Aristides Agramonte, U. S. Army;

Acting Assistant Surgeon Jesse W. Lazear, U. S. Army.

The board will act under general instructions to be communicated to Major Reed by the Surgeon General of the Army.

By command of MAJOR GENERAL MILES,

H. C. COBBIN,

Adjutant General

Memorandum, George Miller Sternberg to Walter Reed May 29, 1900

719861 Communications on official business should be addressed, "To the Surgeon General, U. S. Army, Washington, D. C."

Subject:

WAR DEPARTMENT.

In reply refer to No.

RECORDED

Surgeon General's Office,

Washington, May 29, 1900.

Major Walter Reed,
Surgeon, U. S. Army,
Curator, Army Medical Museum,
Surgeon General's Office, Washington, D. C.

Sir:-

As President of the Board constituted for the purpose of making investigations with reference to the infectious diseases prevailing in the island of Cuba (paragraph 34, S. O. 122, A. G. O., May 24, 1900), you will be governed by the following instructions:

This order does not relieve Acting Assistant Surgeons Lazear and Agramonte from the duties to which they are at present assigned, but they are expected to render such assistance as may be practicable in carrying out the investigations contemplated.

Upon arriving in Cuba you should report in person to Major General Wood and inform him as to the objects of your investigation and the nature of your instructions. He will no doubt do everything in his power to assist you. I understand that there is a well-equipped laboratory at Camp Columbia, where Acting Assistant Surgeon Lazear is stationed, and another at Military Hospital Number One, where Acting Assistant Surgeon Agramonte is on duty. No doubt both of these laboratories will be placed at your disposition, and you are at liberty to make your headquarters at either one which may seem to you best suited for your purpose.

You will naturally give special attention to questions relating to the etiology and prevention of yellow fever. As you are familiar with what has already been done by other bacteriologists in this field of investigation, I do not consider it necessary to give you any suggestions or detailed instructions. But it is evident that the most important question which will occupy your attention is that which relates to the etiology of this disease.

You will also take advantage of such opportunities as may offer for the study of other infectious diseases, and especially of the malarial fevers prevailing in the island of Cuba. An important question in connection with the diseases of tropical and semi-tropical countries relates to the etiology of febrile attacks of short duration to which strangers are especially subject. Should you have time there will be ample opportunity for the study of leprosy, in the Leper's Hospital in the city of Havana. Attention should also be given to the infectious diseases of the lower animals, in case any such prevail, the etiology of which has not been definitely determined.

You are authorized to obtain from the Medical Supply Depot in Havana such articles as you may require, upon requisitions approved by the Chief Surgeon, Division of Cuba. Necessary articles not on hand in that Depot should be called for upon special requisitions to be sent to this office.

Very respectfully,

G. M. Sternberg
Surgeon General, U. S. Army.

Biography of Walter Reed

Walter Reed was born in Virginia in 1851. After the Civil War, he entered the University of Virginia, at age 15, with his two older brothers. After about a year, he realized that his father could not support all three boys at the same time, so he got the medical faculty to agree that he could get a medical degree as soon as he passed all the courses. They hardly took him seriously. But he quickly demonstrated what would become a life long trait of application and hard work. He received his MD degree in 1 year, graduating on July 1, 1869, at 17. He remains their youngest graduate ever. He sought additional training and experience in New York City at Bellevue Hospital Medical School where he earned his second MD degree at age 18, although it was not awarded until after he had turned 21. He worked for several years in New York City but ultimately sought a position in the Medical Corps of the U.S. Army. He was commissioned on July 2, 1875.

He spent more than half of his first 20 years on active duty on the American frontier. He and his young wife, Emilie, spent 4 years in Arizona (two locations), 5 years in Nebraska (three locations), and 2 years in Minnesota. In between the frontier assignments, they had assignments in the east and south. During his assignments in the Baltimore and Washington areas, he seized the opportunity given him to study bacteriology and pathology at Johns Hopkins under men who would become giants of American medicine, Welch, Osler, Kelly, and Halsted.

His assignment in 1893 to Washington, DC, as Curator of the Army Medical Museum following the legendary John Shaw Billings, was approximately his 15th change of station move. A recently promoted Major, he was also appointed one of four professors at the new Army Medical School. Created by Surgeon General George Miller Sternberg, the purpose of the Army Medical School was to take graduates of civilian medical schools and prepare them for the practice of military medicine. Reed had no formal teaching experience and only one scientific publication but possessed a wealth of military medical experience. Again with application and hard work, he became a respected professor and scientist.

At the Army Medical School his association with Dr. James Carroll flourished as they worked together developing their own laboratory skills as well as courses in pathology and bacteriology. Reed's work and writings showed accuracy and originality. His military experience and excellent judgment made him a particularly valuable asset in investigating epidemics and in



making sanitary inspections. Over the years, Reed became a trusted troubleshooter for the Surgeon General.

During the brief Spanish-American War, more volunteer troops died in their American training camps from disease, especially typhoid, than were killed by the enemy. Reed was selected by the Surgeon General to head a commission to study this scandalous issue. The investigative work of the U.S. Army Typhoid Board consumed over a years time. Their findings revolutionized the Army's approach to contaminated materials, water, and waste.

Following the war, yellow fever loomed as a significant problem for the U.S. Army in its planned 4 year occupation of Cuba. In 1899, Reed and Carroll published a paper refuting the claim of the respected Italian scientist Guiseppe Sanarelli that a bacterium he had discovered was the agent of yellow fever. Surgeon General Sternberg, the country's leading expert on yellow fever, agreed with them completely. As the yellow fever season of 1900 approached and the sanitary measures taken to protect the forces in Cuba were clearly less than adequate, Sternberg appointed a group of Army physicians to study the issue. Major Walter Reed was the obvious choice to head the team. Their orders were issued May 23, 1900. A month later they held their first meeting on the veranda of the Officers Quarters at Camp Columbia, Cuba.

Biography of James Carroll

Born in England in 1854, James Carroll immigrated to Canada in his early teens. There he worked as a woodsman for several years before coming to the U.S. and enlisting in the U.S. Army in June 1874. He served as a private, corporal, sergeant, and hospital steward with numerous assignments on the western frontier. During his third enlistment, at age 30, he became interested in the field of medicine and began a quest that culminated 7 years later when he was awarded the MD degree from the University of Maryland in April 1891.

Even though he now possessed a medical degree, he remained a sergeant in the Army. While doing post-graduate work in bacteriology at Johns Hopkins Hospital he worked under Dr. William Welch and assisted Major Walter Reed, another Welch pupil, in his laboratory work.

In 1895 he was assigned to the Army Medical Museum in Washington, DC. Major Walter Reed was Curator of the Army Medical Museum and a professor at the Army Medical School. They worked together at the museum and on several special projects assigned them by Surgeon General George Miller Sternberg. One of these collaborations investigated the 1897 proposal by Sanarelli that he had discovered the causative agent of yellow fever, the *Bacillus icteroides*. Reed and Carroll's work convinced them the *Bacillus icteroides* was identical to the hog cholera bacillus and was not the causative agent of yellow fever.

In May 1898, shortly after Congress declared war on Spain, Carroll was appointed as a Contract Acting Assistant Surgeon in the U.S. Army.

Despite the work of Reed and Carroll on Sanarelli's misidentification of the *Bacillus icteroides* as the cause of yellow fever, there were others of note that still supported this theory. A Presidential commission was appointed, and two respected members of the U.S. Marine Hospital Service (later the Public

Health Service), Drs. Eugene Wasdin and Henry D. Geddings went to Havana to study the issue. They quickly reported their confirmation of Sanarelli's claim. In addition to his need to protect the American troops in Cuba from yellow fever, Sternberg was anxious to put this issue to rest, once and for all. He appointed his own board.

Because of his training, experience, and association with Walter Reed, Carroll was appointed the second in charge of the U.S. Army Board and sailed to Cuba with Major Reed in June 1900.



Method of infecting mosquitoes, originally used by Dr. Lazear. The tube containing the mosquitoes is applied upon the abdomen of the patient. This photograph and caption appeared in Dr. Aramonte's article "The Inside Story of a Great Medical Discovery" published in the Scientific Monthly, December 1915, pages 209-237.

Biography of Aristides Agramonte

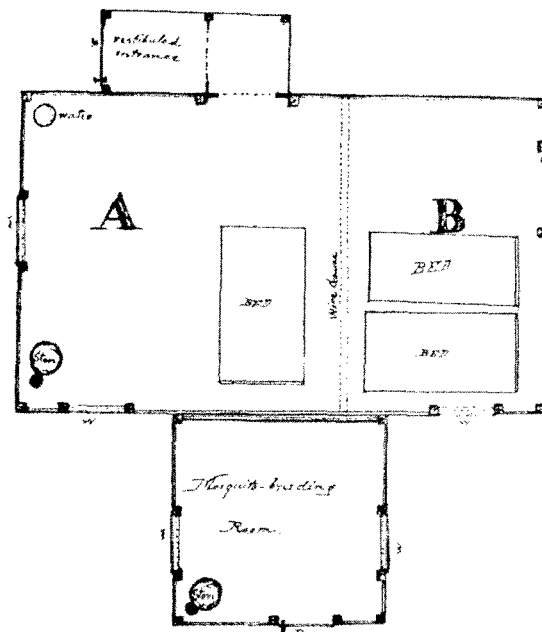
Aristides Agramonte was born in Cuba in 1868 but emigrated to United States at age 3 after his father, General Eduardo Agramonte, was killed in the First Cuban War for Independence. He studied at the College of the City of New York, and he attended medical school at Columbia University. He graduated with honors in 1892. He remained in New York City working in several different positions for the city and the health department. At the time the Spanish American War broke out in 1898, he was an assistant bacteriologist in the New York Health Department.

In May 1898 he was appointed Acting Assistant Surgeon, Medical Corps, U.S. Army and was sent to Santiago de Cuba to study yellow fever. Although he had no recollection or knowledge of having had yellow fever as a child, he was generally thought to be immune to yellow fever because he had been born in Cuba. During this campaign he autopsied numerous cases of yellow fever and could not convincingly confirm the presence of Sanarelli's *Bacillus icteroides*, finding it less than one-third of the time. However, others were still supporting Sanarelli's claim. Agramonte was later sent by Surgeon General Sternberg to Havana in hopes of clearing up this issue.

Governor General Leonard Wood had ordered that Havana be cleaned up in order to improve the public health. The incidence of many diseases including smallpox, typhoid, and dysentery declined sharply but yellow fever seemed unaffected. In May 1900 Agramonte was placed in charge of the division laboratory



at Military Hospital Number One in Havana located next to the University of Havana. That same month, he was appointed to the U.S. Army Board headed by Major Reed.



Plan of the "Mosquito Building" at Camp Lazear. The man who for a short time occupied the bed in room marked "A" became infected by the bites of mosquitoes previously introduced, while those, equally susceptible, who occupied beds in the section marked "B" remained in good health. Only a wire screen partition separated the two compartments. This photograph and caption appeared in Dr. Agramonte's article, "The Inside Story of a Great Medical Discovery" published in *The Scientific Monthly*, December 1915, pages 209-237.

Biography of Jesse W. Lazear

Jesse W. Lazear was born in Baltimore, Maryland in 1866. After 2 years at Washington and Jefferson College in Pennsylvania, he graduated from Johns Hopkins University and attended medical school at Columbia University, New York City, graduating in 1892 in the same class as Aristides Agramonte. After successfully competing for a position, he remained in New York working at Bellevue Hospital for 2 years. He then spent a year studying under several renowned professors in the great European capitals of Berlin, Paris, and Rome.

In 1895, he returned to Baltimore and became Instructor in Clinical Medicine and head of clinical laboratories at the new Johns Hopkins University School of Medicine. In this position he worked with William Welch and William Osler. In 1898 he developed a method to stain the malaria parasite. He worked with William Thayer on the recently established relationship, made by British Major Ronald Ross of the Indian Health Service, between the *Anopheles* mosquito and malaria. He also published papers on gonorrheal endocarditis and septicemia and the pathology of malaria.

In early 1900, his interest in tropical diseases lead him to apply to the U.S. Army for a temporary assignment to study them. His letter came with a strong supporting recommendation from William Welch and thus received a positive response from Army Surgeon General Sternberg. With his background in laboratory medicine, Sternberg knew that Lazear would be useful in Cuba where he had no one to be in charge of the laboratory at Camp Columbia. Lazear accepted this position and sailed for



Cuba with his wife and infant son in February 1900. Mrs. Lazear was soon to learn that she was pregnant with their second child, and she and their son returned to the U.S. in April 1900.

Because of his expressed interest in tropical diseases and his extensive laboratory experience, Lazear was chosen to be a member of the U.S. Army Board headed by Major Reed.



Method of feeding blood to mosquitoes, also used later for infecting them and for applying the insects to those who were inoculated. This photograph and caption appeared in Dr. Agramonte's article "The Inside Story of a Great Medical Discovery" published in *The Scientific Monthly*, December 1915, pages 209-237.

Historical background: Major Walter Reed and Dr. James Carroll arrived in Cuba on June 25, 1900 and held the first meeting of the U.S. Army Yellow Fever Board that same day. Drs. Agramonte and Lazear, already in Cuba, joined them on the veranda of the Officers Quarters at Camp Columbia, also called Columbia Barracks. Reed, as president of the Board, was by far the senior officer and most experienced physician of the group. He probably dominated the conversation that afternoon, laying out his plans for their future work. He told them he thought they would be involved in this work for 1 to 2 years. It is clear that his intentions were to further investigate the possibility that the *Bacillus icteroides* was the causative agent of yellow fever. In the month since the orders for the Board had been issued, they had certainly been reading and re-reading everything they could find on yellow fever. They all knew there were many theories on the etiology to include, most prominently, bacteria and fomites, articles of clothing, and bedding contaminated by sick yellow-fever patients.

The junior officers must have been excited and honored to be named to such an important work and were probably bursting with thoughts and ideas. In addition to the previous Reed and Carroll work on the Sanarelli claim, Agramonte had also unsuccessfully tried to corroborate the theory. However, the recent report by Drs. Wasdin and Geddings of the U.S. Marine Hospital Service had supported Sanarelli, and Reed knew this issue had to be addressed first.

They were all aware of the work of British Major Ronald Ross in proving the mosquito vector in malaria. They were also knew of the article by Dr. Henry R. Carter, the Marine Hospital Service's Chief Quarantine Officer for Cuba that put forth the idea of an "extrinsic incubation period." Dr. Lazear had worked with malaria and mosquitoes in Baltimore. As both were in Havana, it is reasonable to assume that Carter and Lazear had previously met and discussed yellow fever. How much Lazear spoke during that first meeting of the Board, in the presence of the respected and senior Reed, is not recorded. It is clear from the note shown here (Fig. 1) that Carter and Lazear had discussed the mosquito theory. It had been 2 years since Carter had studied the Mississippi epidemic, and in the interim he apparently had moved toward the idea of an intermediate host, possibly the mosquito. Lazear is credited by some as being the member of the Board with the most interest and enthusiasm for the mosquito-vector theory. However, with the other issues to settle first, it would be over a month before the Board began to seriously consider the mosquito theory.

"Salebes" mentioned in the last sentence may have been Dr. Najeb M. Saleeby, a contract surgeon serving with the U.S. Army in Cuba. (Document courtesy of the National Library of Medicine.)

Memorandum: Henry R. Carter to Jesse Lazear, Undated

My dear Dr. Lazear:
 I think that this is about the argument I made
 to you yesterday & which you can, rather ally examine
 better when written out. As I said; to me the a-
 priori argument for Dr. F's theory has much in
 its favor to me is more than plausible - yet
 although his observations, as I have read them are
 not convincing, scarcely corroborating, I pin this on the
 fourth list, which I will ask you to return. Carter
 I have two others.
 Also append a somewhat "list
 of hours"
 Salebes I suppose is gone?
 H. R. Carter

*Returned by Dr. Lazear
 to Dr. Carter with letter #4, 1/2, 1/2
 Jan. 5/01
 (See on above)*

Dear Doctor Lazear:

I think that this is about the argument I made to you yesterday and which you can, naturally, examine better when written out. As I said; to me the a-priori argument for Dr. F's [Finlay] theory has much in its favor and to me is more than plausible, although his observations as I read them are not convincing,

scarcely corroborative. I pin this on the pamphlet which I will ask you to return as I have no other. Also appended a more readable "list of hours."

Salebes, I suppose, is gone?

H.R. Carter

Historical background: The initial work of the Board was aimed at the theory that *Bacillus icteroides* was the causative agent of yellow fever. The yellow fever epidemic currently raging in Havana and the surrounding area gave them plenty of clinical material and they rather quickly gathered enough blood culture and autopsy data to dismiss Sanarelli's claim. After a trip to Pinar del Rio in western Cuba, Reed and Agramonte had been impressed by the case of a single prisoner who, while in a cell with eight others, came down with yellow fever. Because his cellmates had remained well, they began to wonder if maybe there was something to Dr. Carlos Finlay's mosquito theory. With Dr. Henry R. Carter's work also in mind, the members of the Board met and discussed the issue. Despite Dr. Finlay's lack of success with over 100 attempts to transmit yellow fever to humans by the bites of mosquitoes, they decided to visit him. The members also discussed self-experimentation with the mosquitoes, and all decided they would participate.

The work on the report of the U.S. Army Typhoid Board had slowed down after the unexpected death of Board member E. O. Shakespeare. Reed was called back to Washington, DC to complete the report with remaining Board member, Victor Vaughn. He sailed from Havana on August 2, 1900 aboard the transport Rawlins.

Carlos Finlay, who knew of the Board's presence at Camp Columbia, must have been thrilled to see them interested in his theory. He gave them some mosquito eggs along with instructions on how to care for them. Lazear, who may have been the first to push for this line of investigation, was the obvious choice for this work.

In August 1900, 10 volunteers including Lazear were bitten by mosquitoes that had been "loaded" by feeding on patients acutely ill with yellow fever. Lazear recorded meticulous notes in his notebook that would be critical to ultimately solving the puzzle. Lack of immediate success discouraged them, and they began to doubt any positive results with the mosquitoes. Probably thinking it was useless to continue to follow this course of investigation but to keep one of their "loaded" mosquitoes alive, Carroll was bitten on August 27. In the evening 3 days later he was not feeling well, and the following day he knew he was sick, which he thought was malaria. When examinations of his blood that evening and the next morning were negative for malaria, all of them were horrified to realize that he had yellow fever. At noon on September 1, 1900 he was taken to the yellow fever ward at Columbia Barracks. Several days of deathly illness followed, but a week later he began to improve. This letter (Fig. 1) was written by Walter Reed from Washington, DC on September 7, 1900.

Letter: Walter Reed to James Carroll, September 7, 1900*

WAR DEPARTMENT,
SURGEON GENERAL'S OFFICE,
WASHINGTON.
 (over) Sept. 7, 1900
 1.15 P.M.
 My Dear Carroll:
 Hip! Hip! Hurrah! God be praised for the news from Cuba today — "Carroll much improved — Prognosis very good"! I shall simply go out and get boiling Drunk!
 Really I can never recall such a sense of relief in all my life, as the news of your recovery gives me! And then too, would you believe it? The Typhoid Report is on its way to the upper office!
 Well, I'm damned if I don't get drunk twice!!!
 God bless you, my boy.
 Affectionately,
 Come home as soon as you can and see your wife and babies.
 You can see your wife and babies.

Did the Mosquito do it?

Sept. 7, 1900

1.15 p.m.

(over)

My Dear Carroll:

Hip! Hip! Hurrah! God be praised for the news from Cuba today — "Carroll much improved — Prognosis very good"! I shall simply go out and get boiling Drunk!

Really I can never recall such a sense of relief in all my life, as

the news of your recovery gives me! And then too, would you believe it? The Typhoid Report is on its way to the upper office!

Well, I'm damned if I don't get drunk twice!!!

(over)

God bless you my boy.

Affectionately,

Reed

Come home as soon as you can and see your wife and babies.

[Written on the envelope:]

Did the Mosquito do it?

* Original letter courtesy of Dr. Theodore E. Woodward.

Historical Background: Reed had been back in the U.S. during August and September 1900 finishing the report of the Typhoid Board. While in Washington, DC, he no doubt discussed their early results and plans for further experiments with Surgeon General Sternberg. Jesse Lazear had become ill with yellow fever on September 18 and died on the 25th. Following this tragic event, Reed returned to Cuba arriving on October 3, 1900. Despite his grief over Lazear's death and his shock to see Carroll still quite ill, he felt they had enough information to make a preliminary report and wanted to get their data presented as quickly as possible as he knew other researchers were working on these same questions. In an incredible 10 days he wrote and prepared this paper, got permission to travel to Indianapolis to present it, and got backing for further experiments from the Military Governor of Cuba, Major General Leonard Wood. Reed departed on October 14, 1900 and presented this paper before the American Public Health Association during its annual meeting, October 22-26, 1900. It was reprinted in their Proceedings and published in the *Philadelphia Medical Journal* on October 27, 1900. The name of the *Culex* mosquito was changed to *Stegomyia* and is now, *Aedes aegypti*. Case 11, only identified as X.Y., was later revealed to be Private William H. Dean of the Seventh Calvary. Reed chose not to disclose his identity in the paper because Dean's commanding officer was not asked if Dean could participate in the experiment. Dean's was the first truly controlled experimental case of yellow fever.

The Etiology of Yellow Fever — A Preliminary Note

Walter Reed, MD, Surgeon, United States Army, James Carroll, MD, A. Agramonte, MD, and Jesse W. Lazear,¹ MD, Acting Assistant Surgeons, United States Army

The writers, constituting a board of medical officers, convened "for the purpose of pursuing scientific investigations with reference to the acute infectious diseases prevalent on the Island of Cuba," arrived at our station, Columbia Barracks, Quemados, Cuba, on June 25 of the present year, and proceeded under written instructions from the Surgeon General of the Army, to "give special attention to questions relating to the etiology and prevention of yellow fever."

Two of its members (Agramonte and Lazear) were stationed on the Island of Cuba, the former in Habana, and the latter at Columbia Barracks, and were already pursuing investigations relating to the etiology of this disease.

Fortunately for the purposes of this board, an epidemic of yellow fever was prevailing in the adjacent town of Quemados, Cuba, at the time of our arrival, thus furnishing us an opportunity for clinical observations and for bacteriologic and pathologic work. The results already obtained, we believe, warrant the publication, at this time, of a preliminary note. A more detailed account of our observations will be submitted to Surgeon General Sternberg in a future report.

The first part of this preliminary note will deal with the results of blood cultures during life and of cultures taken from yellow fever cadavers; reserving for the second part a consideration of the mosquito as instrumental in the propagation of yellow fever; with observations based on the biting of nonimmune human beings by mosquitoes which had fed on patients sick with yellow fever, at various intervals prior to the biting.

In prosecuting the first part of our work, we isolated a variety of bacteria, but of these we do not propose to speak at present. It will suffice for our purpose if we state the results as regards the findings of *Bacillus icteroides*, leaving the mention of other bacteria to our detailed report.

The cases studied during the Quemados epidemic had been diagnosed by a board of physicians selected by reason of their familiarity with yellow fever. This board consisted of Drs. Nicola Silverio, Manuel Herrera, Eduardo Angles, and Acting Asst. Surgs. Roger P. Ames and Jesse W. Lazear, U.S. Army.

Those studied in Habana were patients in Las Animas Hospital and had been diagnosed as such by a board of distinguished practitioners of that city.

An examination of Table I will show the character of the attacks.

The milder cases studied, few in number, were attended by jaundice and albumin in the urine.

Bacillus Icteroides (Sanarelli) as the Cause of Yellow Fever

The claim of Sanarelli for the specific character of *B. icteroides* as the causative agent in yellow fever, has excited such wide attention, since the publication of his observations, that it seemed to us of the first importance to give our undivided attention to the isolation of this microorganism from the blood of those sick with yellow fever, and from the blood and organs of yellow-fever cadavers.

Cultures Taken from the Blood during Life

The method followed was that ordinarily used in an attempt to isolate bacteria from the circulating blood; viz., from a vein at the bend of the elbow, a sufficient quantity of blood was taken with an hypodermic syringe, made sterile by boiling, and after careful cleansing of the skin with soap and water, followed by equal parts of absolute alcohol and ether, and 1:2000 bichloride solution.

Exceptionally the blood withdrawn was plated on agar, but, as a rule, it was immediately transferred to sterile bouillon tubes (10 c.c.) in quantities of 0.5 c.c. to each of several tubes. These were then incubated at from 35° to 37°C. for a period of one week. They were examined daily and if growth was observed, plates in agar or gelatin, or both, were made and the colonies carefully studied by transference to ordinary laboratory media.

Eighteen cases have thus been carefully studied; of these 11 were designated as "severe" cases of yellow fever with 4 deaths, three as "well-marked" cases with no deaths, and 4 as "mild" cases with no deaths.

From these 18 cases blood-cultures were made, as shown in Table I:

It will be seen that of 48 separate cultures made from the blood on various days of the disease and representing 115 bouillon inoculations and 18 agar plates, we failed to find *Bacillus icteroides* in any of our tubes or plates.

The results of cultures taken in 18² cases of unmistakable yellow fever, on various days of the disease, and in some cases on every day from the onset to death or recovery, would seem to exclude the presence of *Bacillus icteroides* in the blood of these cases during life.

It will therefore be seen that while Wasdin and Geddings taking cultures from the ear lobe (Report on the Cause of Yellow Fever, 1899), record that "in the blood of yellow fever cases extracted during life *Bacillus icteroides* has been found in 13 of the 14 cases, with 1 negative" (92.85 per cent), we, by withdrawing blood from the veins of 18 patients, have to record 100 per cent of failures.

We have already stated that we will reserve for a later report a description of the bacteria isolated from the blood in these cases. We now remark that but few organisms were obtained and that, as a rule, our blood cultures gave no growth whatever.

Cultures from Yellow Fever Cadavers

We tried to obtain autopsies very soon after death, and sometimes succeeded in doing so. Tubes containing about 10 c.c. of flesh-peptone bouillon were generally used for the first inoculation direct from the blood and organs. As soon as the laboratory was reached, agar plates were made from these inoculated bouillon tubes, the former as well as the latter being then incu-

bated at from 35°-37°C. In nearly every case gelatin plates were also made from the recently inoculated bouillon tubes and kept at a temperature of 19°-20°C.

If colonies were found in the agar or gelatin plates, on the following days, the corresponding bouillon tubes were also plated on agar and gelatin. The bacteria thus found in our plates were carefully isolated and studied upon the usual nutritive media, so as to enable us to identify them, if possible. We will here content ourselves with giving the results as regards the presence of *B. icteroides* only (Table II).

Our failure to isolate *B. icteroides* in these 11 autopsies of yellow-fever patients was a result which we had not anticipated. One of us (Agramonte), who, at Santiago, Cuba, during the epidemic of 1898, succeeded in finding *B. icteroides* in 33% of his autopsies, has been much surprised at the absence of this bacillus in cultures from cadavers sectioned in or near Habana, during the present year. In 2 of the 11 cases we had reason to believe that from the appearance of colonies seen in gelatin plates, we would be able to isolate *B. icteroides*. These colonies, however, when transferred to other media and carefully studied, did not prove to be this bacillus. We wonder whether other observers have occasionally relied upon the appearance of colonies in gelatin plates, without further study. We only mention this as a possible explanation of the large percentage of positive results recorded by some observers.

Pothier, of New Orleans, La., only succeeded, however, in isolating *B. icteroides* in 3 out of 51 autopsies. (*Journal of American Medical Association*, Apr. 16, 1898.)

Lutz (*Revista D'Igiene e Santia Publica*, XI, No. 13, July 1900, pp. 474-475) says, as the results of his extensive observations

TABLE I
BLOOD-CULTURES DURING LIFE

Days of Disease	Character of Attack	No. of Cultures	No. of Bouillon Tubes Inoculated	<i>Bacillus icteroides</i>
1st	Severe	3	4 (3 agar plates)	Negative
"	Well marked	1	4	"
"	Mild	1	3	"
2d	Severe	6	18	"
"	Well marked	1	2	"
"	Mild	1	3 (6 agar plates)	"
3d	Severe	7	18 (6 agar plates)	"
"	Mild	2	4	"
4th	Severe	5	14	"
"	Well marked	2	6	"
"	Mild	1	1	"
5th	Severe	5	12 (3 agar plates)	"
"	Well marked	1	3	"
"	Mild	1	1	"
6th	Severe	4	6	"
"	Well marked	1	2	"
7th	Severe	1	2	"
"	Well marked	1	2	"
8th	Severe	2	6	"
"	Well marked	1	2	"
9th	Severe	1	2	"

Number of cultures . . . 48.

Number of bouillon tubes inoculated . . . 115.

Number of agar plates . . . 18.

TABLE II

No. of Case	Day of Disease	Time of Autopsy	Source of Culture	<i>B. icteroides</i>
1	Seventh	2 hours after death	Blood, liver, spleen, kidney	Negative
2	Sixth	13 hours after death	Blood, liver, spleen, kidney	"
3	Fourth	8 hours after death	Blood, liver, spleen, kidney	"
4	Eighth	2 hours after death	Abdominal cavity, blood, liver, spleen, kidney, bile, duodenum	"
5	Fourth	4 hours after death	Blood, liver, spleen, kidney, bile, duodenum	"
6	Sixth	6 ½ hours after death	Abdominal cavity, blood, pericardial fluid, lung, spleen, kidney, liver, bile duodenum	"
7	Sixth	50 minutes after death	Blood, lung, liver, spleen, kidney, bile, jejunum	"
8	Sixth	½ hour after death	Blood, lung, liver, spleen, kidney, urine, small intestine	"
9	Fourth	2 hours after death	Liver, spleen, small intestine	"
10	Fifth	7 hours after death	Liver, kidney, spleen, small intestine	"
11	Third	½ hour after death	Liver, kidney, spleen	"

on yellow fever, that *Bacillus icteroides* cannot be found by present laboratory methods in more than half of the cases of yellow fever, and that when present the colonies are few in number.

It is possible that our future autopsies may give more favorable results as regards *B. icteroides*.

The Mosquito as the Host of the Parasite of Yellow Fever

Having failed to isolate *B. icteroides*, either from the blood during life, or from the blood and organs of cadavers, two courses of procedure in our further investigations appeared to be deserving of attention, viz., first, a careful study of the intestinal flora in yellow fever in comparison with the bacteria that we might isolate from the intestinal canal of healthy individuals, in this vicinity, or of those sick with other diseases; or, secondly, to 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 Habana, in 1881 (*Anales de la Real Academia*, vol. 18, 1881, pp. 147-169).

We were influenced to take up the second line of investigation by reason of the well-known facts connected with the epidemiology of this disease, and, of course, by the brilliant work of Ross and the Italian observers, in connection with the theory of the propagation of malaria by the mosquito.

We were also very much impressed by the valuable observations made at Orwood and Taylor, Miss., during the year 1898, by Surg. Henry R. Carter, U.S. Marine-Hospital Service. A note on the interval between infecting and secondary cases of yellow fever, etc., (Reprint from *New Orleans Medical Journal*, May 1900). We do not believe that sufficient importance has been accorded these painstaking and valuable data. We observe that the members of the yellow fever commission of the Liverpool School of Tropical Medicine, Drs. Durham and Meyers, to whom we had the pleasure of submitting Carter's observations, have been equally impressed by their importance (*British Medical Journal*, September 8, 1900, pp. 656-657.)

The circumstances under which Carter worked were favorable for recording with considerable accuracy the interval between the time of arrival of infecting cases in isolated farmhouses and the occurrence of secondary cases in these houses. According to

Carter, "the period from the first (infecting) case to the first group of cases infected, at these houses, is generally from two to three weeks."

The houses having now become infected, susceptible individuals thereafter visiting the houses for a few hours, fall sick with the disease in the usual period of incubation—one to seven days.

Other observations made by us since our arrival confirmed Carter's conclusions, thus pointing as it seemed to us to the presence of an intermediate host, such as the mosquito, which having taken the parasite into its stomach, soon after the entrance of the patient into the noninfected house, was able after a certain interval to reconvey the infecting agent to other individuals, thereby converting a noninfected house into an "infected" house. This interval would appear to be from 9 to 16 days (allowing for the period of incubation), which agrees fairly closely with the time required for the passage of the malarial parasite from the stomach of the mosquito to its salivary glands.

In view of the foregoing observations we concluded to test the theory of Finlay on human beings. According to this author's observation of numerous inoculations in 90 individuals, the applications of one or two contaminated mosquitoes is not dangerous, but followed in about 18 per cent, by an attack of what he considers to be very benign yellow fever at most.

We here desire to express our sincere thanks to Dr. Finlay, who accorded us a most courteous interview and has gladly placed at our disposal his several publications relating to yellow fever during the past 19 years; and also for ova of the variety of mosquito with which he had made his several inoculations. An important observation to be here recorded is that, according to Finlay's statement, 30 days prior to our visit, these ova had been deposited by a female just at the edge of the water in a small basin, whose contents had been allowed to slightly evaporate; so that these ova were at the time of our visit entirely above contact with the water. Notwithstanding this long interval after deposition, they were promptly converted into the larval stage, after a short period, by raising the level of the water in the basin.

With the mosquitoes thus obtained we have been able to conduct our experiments. Specimens of this mosquito forwarded to Mr. L.O. Howard, entomologist, Department of Agriculture, Washington, D.C., were kindly identified as *Culex fasciatus*, Fabr.

In this preliminary note we have not space to refer, at length, to the various interesting and valuable contributions made by Finlay to the mosquito theory for the propagation of yellow fever. In addition to the paper already quoted, his most valuable contributions to this important theory are to be found in the articles designated as follows: *Estadística de las Inoculaciones con mosquitos contaminados*, etc., reprint, Habana, 1891; *Fiebre Amarilla, Estudio Clínico Patológico y Etiológico*, reprint, Habana, 1895; and *Yellow Fever Immunity-Modes of Propagation-Mosquito Theory*, 8th Congress of International Hygiene and Demography, Budapest, 1894.

His present views on this subject may be stated in his own language: "First, reproduction of the disease, in a mild form, within 5 to 25 days after having applied contaminated mosquitoes to susceptible subjects. Second, partial or complete immunity against yellow fever obtained even when no pathogenous manifestation had followed these inoculations." (*Medical Record*, Vol. 55, No. 21, May 27, 1899.)

Without reviewing the cases regarded as mild forms by the author of this theory, we believe that he has not, as yet, succeeded in reproducing a well-marked attack of yellow fever, within the usual period of incubation of the disease, attended by albumin and jaundice, and in which all other sources of infection could be excluded.

The experiments made by us on 11 nonimmune individuals are embraced in the preceding table, which should be carefully studied.

The mosquito used in all cases was *Culex fasciatus*, Fabr. (Table III).

It will be seen that we record 9 negative and 2 positive results. It is, we think, important to observe that of the 9 failures to infect, the time elapsing between the biting of the mosquito and the inoculation of the healthy subject varied in 7 cases from 2 to 8 days (Nos. 1, 2, 3, 5, 7, and 9) and in the remaining 2 from 10 to 13 days (Nos. 6 and 8).

Five individuals out of the nine who failed to show any result (Nos. 2, 3, 4, 5, and 6) were inoculated by mosquitoes that had bitten very mild cases of yellow fever on the fifth day of the disease, and one individual by a mosquito that had bitten a mild case of yellow fever on the seventh day of the disease. (This latter patient was discharged from the hospital 3 days later.) To this fact may possibly be attributed the negative results. Of the remaining 3 negative cases (Nos. 7, 8, and 9) and which had been inoculated by mosquitoes that had bitten severe cases of the disease, the interval between the bite and the inoculation varied from 2 to 6 days.

In the 2 cases (Nos. 6 and 8) where the interval was respectively 10 and 13 days, the inoculations had been made with

TABLE III
INOCULATION OF NONIMMUNE INDIVIDUALS THROUGH THE BITE OF MOSQUITOS (*CULEX FASCIATUS*)

No. of Case	Age	Nativity	Date of Inoculation	Character of Attack and Number of Patients Bitten	Day of Disease	Time between Infection of Mosquito and Inoculation	No. of Mosquitos	Result	Remarks
1	...	United States	August 11	Mild, 1	Seventh	5 days	One	Negative	
2	...	United States	August 11	Very mild, 1	Fifth	5 days	One	"	
3	24	United States	August 12	Very mild, 1	Fifth	6 days	One	"	
4	20	United States	August 12	Very mild, 1	Fifth	6 days	One	"	
5	24	United States	August 14	Very mild, 1	Fifth	8 days	One	"	
6	34	United States	August 16	Very mild, 1	Fifth	10 days	One	"	
7	22	United States	August 18	Severe, 1	Second	3 days	One	"	
8	20	United States	August 19	Very mild, 1	Fifth	13 days	Two	"	
				Severe, 1	First	3 days			
9	28	United States	August 25	Fatal, 1	Second	6 days	One	Negative	
				Mild, 1	First	4 days			
				Severe, 1	Second	2 days			
10	46	England	August 27	Severe, 1	Second	12 days	One	Positive	Severe attack of yellow fever
				Mild, 1	First	6 days			
				Severe, 1	Second	4 days			
11	24	United States	August 31	Mild, 1	Second	12 days	One	Positive	Well-marked attack of yellow fever
				Fatal, 1	Second	4 and 10 days			
				Mild, 2	Second	4 and 10 days			
				Severe, 2	Second and ninth	2 and 8 days			
				Severe, 3	First, second and second	2, 8 and 16 days	One		
				Mild, 2	First and second	6 and 10 days			
				Fatal, 1	Second	12 days	One		
				Severe, 1	First	2 days			
				Mild, 3	First, second and second	4, 6 and 10 days			
				Severe, 3	All on first	2, 4 and 8 days	One		
				Mild, 1	Second	6 days			

mosquitoes that had bitten very mild cases of yellow fever on the fifth day of the attack. No. 8 was also bitten by a mosquito which had been infected by a severe case of yellow fever 3 days before.

We refrain from commenting further at this time upon the 9 negative cases, preferring to record the results obtained rather than to indulge in speculation.

Of the two cases which we have recorded as positive in Table III, we now propose to speak at greater length.

Case 10

Dr. James Carroll, acting assistant surgeon U.S. Army, a member of this board, was bitten at 2 p.m. August 27, 1900, by *Culex fasciatus*. This particular mosquito has bitten a severe case of yellow fever on the second day of the disease 12 days before; a mild case of yellow fever on the first day of the attack, 6 days preceding; a severe case of yellow fever, on the second day of the attack, 4 days before; a mild case of yellow fever, on the second day of the attack, 2 days before inoculation.

Dr. Carroll remained well until the afternoon of the 29th, when he states that he felt tired and for this reason, when on a visit to Las Animas Hospital, the same afternoon (29th) some time between 4 and 6 p.m., after visiting a few patients, he left the wards and waited outside on the porch, while his companions remained in the wards.

August 30. During the afternoon, although not feeling well, Dr. Carroll visited La Playa, about 1½ miles from Columbia Barracks, and took a sea-bath.

August 31. a.m. Dr. Carroll realized that he was sick and that he had fever, although he refrained from taking his temperature, but did visit the laboratory, distant about 140 yards, for the purpose of examining his blood for the malarial parasite. The examination was negative. During the afternoon he was compelled to take to his bed. At 7 p.m. temperature was 102°F. He had no headache or backache; only a sense of great lassitude. Eyes injected and face suffused.

September 1, 7 a.m. his temperature was 102°. Blood was again carefully examined by Dr. Lazear with negative result. 11 a.m. temperature was 102°. The case having been diagnosed as one of yellow fever, Dr. Carroll was at noon removed to the yellow fever wards. 9 p.m. temperature was 102.8°, pulse 90; 12 o'clock midnight temperature 103.4°, pulse 84.

September 2, 3 a.m. Temperature 103.6°, pulse 80. A trace of albumin was now found in the urine. The subsequent history of the case was one of severe yellow fever. Jaundice appeared on September 3.

The accompanying Chart I contains all of the necessary data.

The question of diagnosis having been clearly and easily established, it now becomes important to follow Dr. Carroll's movements for a period of 10 days preceding the mosquito inoculation, and during the period elapsing from the bite of the insect until the commencement of the attack.

On August 21, 22, and 23, Dr. Carroll was at Columbia Barracks, outside of the epidemic zone. On August 24 he visited the autopsy-room of Military Hospital, No. 1, which is situated on Principe Hill overlooking the city of Habana. He was present in the autopsy-room while an autopsy was made by Dr. Agramonte on a case of pernicious malarial fever. Dr. Carroll only took cultures from the blood and organs as the section proceeded. He was there about half an hour, and then returned to Columbia

Barracks. Subsequent microscopic study of sections of the liver and spleen showed that the case autopsied on the 29th was really a case of pernicious malarial fever.

It should be stated that although cases of yellow fever are not admitted to Military Hospital No. 1., an English sea-captain had been admitted to its wards a few days before, whose case developed into one of yellow fever with fatal results, and autopsy had been held upon the body by Dr. Agramonte in this death room on the day preceding Dr. Carroll's visit to it.

According to Dr. Carroll, the room was by no means in a cleanly condition. As Dr. Carroll's visit to this room was made on August 24, and as he began to complain on August 29, about the average period of incubation of yellow fever, there is a possible chance for infection in this way. We must call attention, however, to the fact that Dr. Agramonte, whenever he performs an autopsy in this room, is always attended by a young soldier of the Hospital Corps, U.S. Army, who is detailed for that purpose, and whose duty it is to assist and afterwards to tend to the cleaning of the autopsy table. This soldier, a nonimmune American, was present when Dr. Carroll was there, and remained afterward to attend to his duties. He has not contracted yellow fever by his duties in this room from day to day. Our own experience would seem to accord with others, viz., that attendance upon autopsies and the handling of portions of organs of yellow-fever cases removed to the laboratory is unattended with danger. Certainly the three nonimmune members of this board, up to the time of these mosquito inoculations had, during the past three months, come in close contact with the dead bodies and organs of yellow-fever cases, freely handling and examining these organs, including the small intestine, even kept at thermostat temperature for 24 hours, without contracting the disease. We have, of course, never neglected to cleanse our hands with disinfectants.

Dr. Carroll, upon his visit to the before-mentioned dead-room, only used the platinum loop for taking cultures, and did not come in contact with the autopsy table.

The only other opportunity for infection in his case would appear to have been during his visit to Las Animas Hospital, situated in the suburbs of Habana, as yellow-fever patients are admitted in large numbers. We have already pointed out that Dr. Carroll was complaining of lassitude at the hour of his visit, which was about 50 hours after his inoculation with the contaminated mosquito. We have also called attention to the fact that he remained, for the greater part of his visit, outside of the hospital, on the piazza. This would appear to cast doubt upon his visit to Las Animas as the source of his infection.

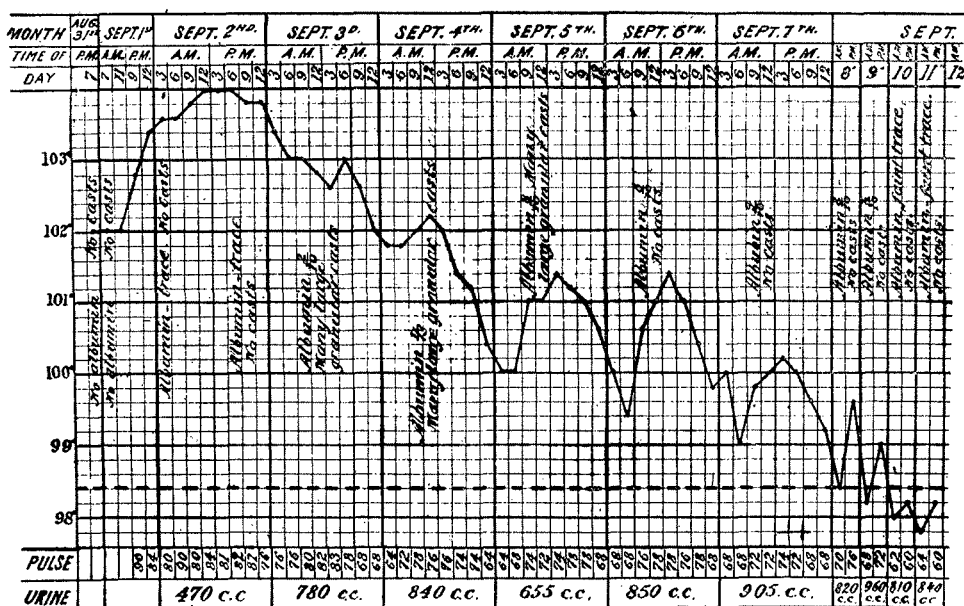
We do not wish to be understood as unnecessarily seeking to lay too much emphasis upon the exclusion in this case of other sources of infection than the mosquito, as we fully appreciate that Dr. Carroll had been on two occasions within the epidemic zone during the week preceding his attack of yellow fever. His movements on these occasions we have already given.

We will again refer to Dr. Carroll's case, after we have given the history of Case No. 11, which we have designated as our second positive result.

Case 11

X. Y., aged 24, white, American, a resident of the military reservation of Columbia Barracks, was bitten during the fore-

Chart I. Yellow fever following, within the usual period of incubation, the bite of an infected mosquito (*Culex fasciatus*).



noon of August 31, 1900, by the same mosquito that had bitten Case 10 (Dr. Carroll) four days before, and which in the meantime had bitten a mild case of yellow fever (first day) two days before being applied to X. Y.

X. Y. was also bitten by a second mosquito that had been applied to a fatal case of yellow fever (second day) 12 days before; and to 2 mild cases (second day) 4 and 10 days previously; also, by a third mosquito that had bitten a fatal case of yellow fever (second day) 12 days before; a severe case (first day) 2 days before, and 3 mild cases (first, second, and second day) 4, 6, and 10 days before; finally by a fourth mosquito that had bitten 3 severe cases of yellow fever (all on first day) 2, 4, and 8 days previously, and 1 mild case (second day) 6 days before. (Vide Table III).

It will be seen that X. Y. was bitten by 4 mosquitoes, 2 of which had bitten severe (fatal) cases of yellow fever 12 days previously; one of which had bitten a severe case (second day) 16 days before and one which had bitten a severe case 8 days before.

September 25, — X. Y. began to experience a sense of dizziness and disinclination to work. This was just 5 days from the time of the mosquito inoculation.

Twenty-four hours later, still dizzy and light-headed in attempting to move about. During the afternoon (sixth day after inoculation), chilly sensations, followed by fever and restlessness during the night.

On the following day (seventh day after inoculation) 8 a.m., temperature was 102.8°F., eyes were slightly injected, face suffused. Patient removed to the yellow fever wards; at 9 a.m. temperature was 103°F pulse 66. A trace of albumin was found in the urine during the afternoon (third day of the attack). This increased during the following days. Conjunctivae slightly jaundiced on the fourth day of the disease, which was more distinct and could be plainly seen on the anterior aspect of the chest on the fifth and following day. Bleeding from the gums was noticed

on the third and subsequent days after admission. Repeated examinations of the blood failed to show any malarial parasites.

The course of the fever, the appearance of albumin in the urine, with jaundice and hemorrhage from the gums, together with the slow pulse, all pointed distinctly to the diagnosis of yellow fever. His attending physician, Dr. Roger P. Ames, U.S. Army, an expert in the diagnosis and treatment of this disease, did not hesitate to diagnose X.Y.'s attack as one of "well pronounced yellow fever." Dr. Ames was not cognizant of the method of inoculation in this case. (Vide Chart II.)

The diagnosis, therefore, not being in doubt, we must follow this patient's movements during the 10 days preceding the bite of the mosquitoes and from this time until 5 days later, when the attack began. It so happens that we can follow X.Y.'s movements for a much longer period. Fifty-seven days prior to his inoculation, he spent a day and night in the city of Habana. Sixteen days before the inoculation, he rode on horseback with 6 other nonimmunes a distance of about 1½ miles toward the seashore and returned to his dwelling, without in the meantime dismounting from his horse. From this time until his complete convalescence was established, he had remained within the immediate vicinity of his home. So that it may be positively stated that X.Y. had not absented himself from the Military Reservation of Columbia Barracks during a period of 57 days prior to his inoculation (with the exception above stated) nor between the date of his inoculation and the establishment of convalescence.

Let us now inquire whether the military reservation of Columbia Barracks is outside of the epidemic zone of yellow fever. To this we answer that since the commencement of the present epidemic of yellow fever in Habana, dating from May 1900, the average monthly population of this station, including civilian employees, has been 1,400, nearly all of whom are young non-immunes.

There have occurred among this nonimmune population from

September 19, Twelve o'clock noon, his temperature was 102.4°, pulse 112. Eyes injected, face suffused; at 3 p.m. temperature was 103.4°, pulse 104; 6 p.m., temperature 103.8° and pulse 106; albumin appeared in the urine. Jaundice appeared on the third day. The subsequent history of this case was one of progressive and fatal yellow fever, the death of our much-lamented colleague having occurred on the evening of September 25, 1900.

As Dr. Lazear was bitten by a mosquito while present in the wards of a yellow-fever hospital, one must, at least, admit the possibility of this insect's contamination by a previous bite of a yellow-fever patient. This case of accidental infection therefore cannot fail to be of interest taken in connection with Cases 10 and 11.

For ourselves, we have been profoundly impressed with the mode of infection and with the results that followed the bite of the mosquito in these three cases. Our results would appear to throw new light on Carter's observations in Mississippi, as to the period required between the introduction of the first (infecting) case and the occurrence of secondary cases of yellow fever.

Since we here, for the first time, record a case in which a typical attack of yellow fever has followed the bite of an infected

mosquito, within the usual period of incubation of the disease, and in which other sources of infection can be excluded, we feel confident that the publication of these observations must excite renewed interest in the mosquito theory of the propagation of yellow fever, as first proposed by Finlay.

From our study thus far of yellow fever, we draw the following conclusions:

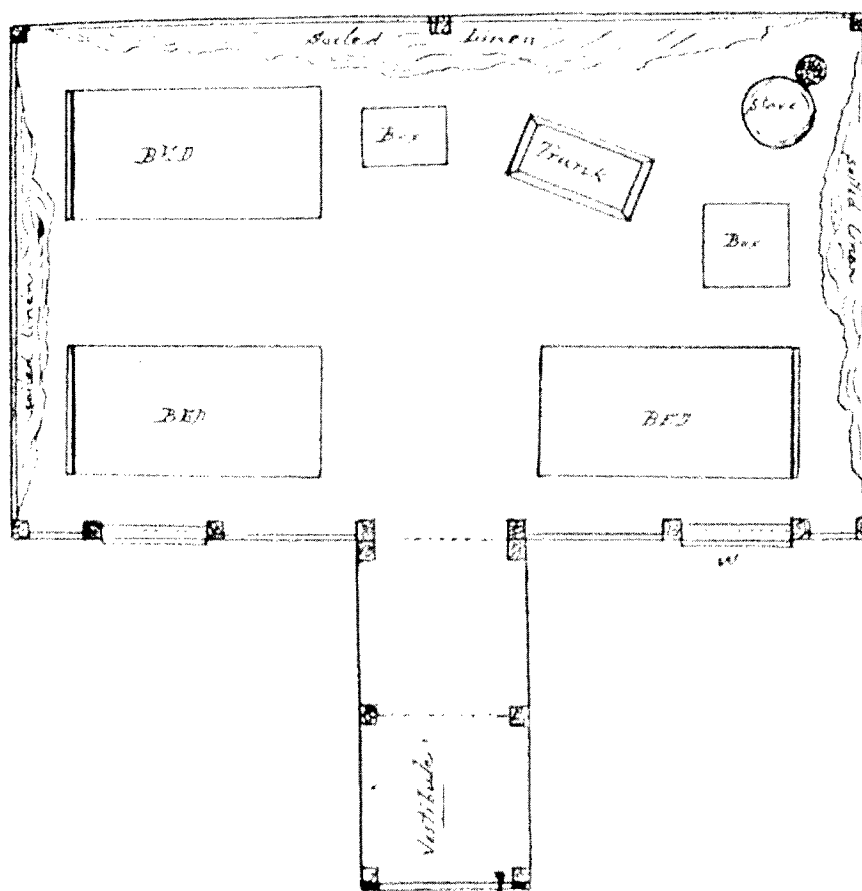
(1) *Bacillus icteroides* (Sanarelli) stands in no causative relation to yellow fever, but, when present, should be considered as a secondary invader in this disease.

(2) The mosquito serves as the intermediate host for the parasite of yellow fever.

[Notes]

¹Died of yellow fever at Columbia Barracks, Cuba, Sept. 25, 1900.

²Cultures from the blood during life had been taken by Dr. Lazear in three other cases of yellow fever, but, owing to the death of our colleague, the necessary data as to the day of the disease on which cultures had been taken cannot be ascertained. These cultures were negative as regards the finding of Sanarelli's bacillus.



Plan of the "Infected Clothing Building" at Camp Lazear. Men who were susceptible to the disease slept many nights in this soiled linen room, without contracting yellow fever. This photograph and caption appeared in Dr. Agramonte's article "The Inside Story of a Great Medical Discovery" published in *The Scientific Monthly*, December 1915, pages 209-237.

Historical Background: Prior to the U.S Army Yellow Fever Board, informed consent was generally not sought and may have even been unknown in human clinical research of this magnitude. In an attempt to produce yellow fever and prove his mosquito theory, Carlos Finlay had conducted experiments on over 90 individuals with over 100 experiments without informed consent. Professor Guiseppe Sanarelli, the Italian scientist working in South America, had claimed in 1897 that he had discovered the causative agent of yellow fever, the *Bacillus icteroides*, and had also claimed the generous reward offered by South American countries for the discoverer of the cause of this dreaded disease. He also reported five attempts to verify his claim by injecting cultures of his bacillus into patients. He did this without permission or consent. Three of his patients died. American physicians and scientists were outraged. Dr. Victor Vaughn, a member of Reed's Typhoid Board, called the experiments "ridiculous." Dr. William Osler went even further and railed, "To deliberately inject a poison of known high degree of virulency into a human being, unless you obtain that man's sanction, is not ridiculous, it is criminal." (Vaughn, V and Osler, W: Discussion of G.M. Sternberg, The *Bacillus icteroides* (Sanarelli) and *Bacillus X* (Sternberg). *Trans. Assoc. Am. Phys.*, 1898, 13:70-71.)

When Walter Reed discussed the plans for experimentation on humans with Surgeon General Sternberg, they most certainly discussed informed consent. It came up during his meeting with Major General Leonard Wood when Reed requested financial support. After inflammatory headlines in a Spanish newspaper in Havana in November 1900, Reed, Carroll, and Agramonte visited the Spanish consul and assured him they were asking only men of majority (24 years old) and getting informed consent before conducting any experiments.

Shown here is a copy of the bi-lingual informed consent contract signed by Antinio Benigno and Walter Reed (Figs. 1 and 2). Dr. Jefferson Randolph Kean described Benigno as "a jolly young Spanish peasant. . . whom Reed called Boniato, which means a sweet potato, on account of his fondness for that vegetable." Benigno was the first Spanish volunteer to contract yellow fever. He recovered. According to Dr. Kean, one of his proud possessions was the original of this contract that hung on his office wall. (Kean, Jefferson R: Walter Reed, Dedication of his Birthplace. *The Military Surgeon* 1928; 62: 301.)

Susan E. Lederer said in her 1995 book, *Subjected to Science*, "they (the consent forms used by the Board) marked a significant departure in the history of human experimentation" (p. 21). Walter Reed biographer, Dr. William Bean, makes an even broader statement when he says that Walter Reed and the U.S. Army Yellow Fever Board were "in a true sense the founder of modern and ethical clinical experimentation" (Bean WB: Walter Reed and yellow fever. *JAMA* 1983; 250: 662.)

Contract between Antonio Benigno and Yellow Fever Board, November 26, 1900*

El que suscribe, *Antonio Benigno*
mayor de veinte y cinco años de edad, natural de *Cereceda*
provincia de *Corona* hijo de *Mmanuel Benigno*
y de *Josefa Castro* hace constar por la presente que, rustoso y
ejerciendo su propia y libre y libre voluntad, consiente en someterse a los
experimentos que con el objeto de determinar las vias de propagacion de
la fiebre amarilla, haga en su persona la Comision que para ese efecto ha
nombrado el Secretario de la Guerra de los Estados Unidos; que a su consenti-
miento para que se lleven a cabo dichos experimentos, por las razones y
con las condiciones que abajo se expresan.

El infrascripto comprende perfectamente bien que en el caso de desar-
rollarse en él la fiebre amarilla, se de perder su vida ante cierto curio
pero siendole completamente imposible evitar el contacto durante su permanen-
cia en este país, creiere arrostrar la posibilidad de contraerla ex-ocresco,
con la seguridad de que no de recibir de la Comision ve mencionados, los
cuidados mas prolijos y la asistencia médica mas esmerosa.

Queda consiguientemente que si terminar esos experimentos antes de transcur-
ridos meses de este fecha, el infrascripto no de recibir la suma de \$ 100...
oro americano y que caso de declararse en él la fiebre amarilla, en cualquier
epoca durante su permanencia en este Campamento, recibirá como de diez
cientos, otra suma de \$100. --oro americano, después de su curacion y que
caso de su fallecimiento por motivo de ese enfermedad, la Comision entregará
dicha cantidad, (ochocientos pesos americanos,) a la persona que él su tiempo
designará el 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 rompiese este compromiso.

Y para su constancia firma este por duplicado, en el Campamento Experi-
mental, cerca de los Cuarteles, Oude, el dia *26* de *Noviembre*
de mil novecientos.

El interesado,

Antonio Benigno

De conformidad, la Comision.

Walter Reed
Major, Army, U.S.A.

* Documents courtesy of the Walter Reed Army Institute of Research.

The undersigned, Antonio Benino *Antonio Benino*
 being more than twenty-five years of age, native of Ceroeda,
 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, made upon his person by the
 Commission appointed for this purpose by the Secretary of War of the
 United States, and that he gives his consent to undergo the said ex-
 periments for the reasons and under the conditions below stated.

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 skill-
 ful medical service.

It is understood that at the completion of these experiments, with-
 in two months from this date, the undersigned will receive the sum of
 \$100 in American gold and that in case of his contracting yellow fever
 at any time during his residence in this camp, he will receive in addi-
 tion to that sum a further sum of \$100 in American gold, upon his re-
 covery and that in case of his death because of this disease, the
 Commission will transmit the said sum (two hundred American dollars)
 to the person whom the undersigned shall designate at his convenience.

The undersigned binds himself not to leave the bounds of this camp
 during the period of the experiments and will forfeit all right to the
 benefits named in this contract if he breaks this agreement.

And to bind himself he signs this paper in duplicate, in the Experi-
 mental Camp, near Quemados, Cuba, on the 26th day of November
 nineteen hundred.

On the part of the Commission:

Walter Reed
 Maj. & Surg., U.S.A.

The contracting party,

Antonio Benigno

Historical Background: Lieutenant Albert E. Truby was a physician assigned to the hospital at Columbia Barracks, Cuba when Walter Reed and James Carroll arrived in the summer of 1900 to begin their work. Truby had met Reed previously as Reed had served on the Examining Board that selected Truby for active duty in 1898. Truby witnessed the initial work of the Board and the opening of Camp Lazear on November 20, 1900. He was reassigned on November 30, 1900 to Rowell Barracks near Cienfuegos, Cuba as Post Surgeon. In this letter (Fig. 1), Reed excitedly reports the mosquito theory to be correct. The first volunteer to become ill at Camp Lazear was Private John R. Kissinger (Reed misspelled his name). The term "birds" refers to their experimental mosquitoes and the number of days refers to how long it has been since that mosquito fed on an infected yellow fever patient. "Cooke and Co." refers to Dr. Robert P. Cooke and two enlisted volunteers that were the first of the brave men to test the fomite theory. Walter Reed's son, Lawrence, was also assigned to Rowell Barracks as a second lieutenant with the 10th Infantry. In an earlier letter Truby had informed Major Reed that he had made contact with his son. Later Brigadier General Albert E. Truby commanded Walter Reed General Hospital and after retirement wrote *Memoir of Walter Reed - The Yellow Fever Episode* published in 1943.

Letter: Walter Reed to Albert E. Truby, December 10, 1900*

Columbia Barracks,
Cienfuegos,
Dec. 10th 1900.

My dear Dr. Truby,
Just
a line to thank you
for the mosquitoes which
came safely several
days ago, (which prove
to be beautiful specimens
of *C. fasciatus*), and, also,
to tell you that the theo-
ry is alright! our
first case came down
in Camp (Kissinger)

on Saturday night -
 was bitten on 5th at
 11.30 am. by two 21 day
 "birds", one 19 day, ~~and~~
one 16 day & one 12 day
 "bird". Initial chill
 11.30 at night, Saturday; ~~just~~
 84 hours (3 1/2 days) follow-
 ing, with rise of T. to
 100°, severe headache and
 backache, ^{with} infected eyes.
 T. at midnight 101° & at
 9 am. 102.2. &c! The
 case is a beautiful one,
 and will be seen by
 the Board of Havana
 Experts, to-day, all of

who are except Finlay, consider
 the theory a wild one!
 Cooke & Co. in infected bedding
 house are enjoying their
 usual health, but much relieved
 when told that C. Fasciatus
 has got in his work! Congratu-
 lations are now in order -
 Love to my boy -
 Sincerely, your friend,
 Walter Reed

Just a line to thank you for the mosquitoes which came safely
 several days ago, (& which proved to be beautiful specimens of
 C. Fasciatus), and, also, to tell you that the theory is alright! Our
 first case came down in Camp (Kissenger) on Saturday night -
 was bitten on 5th at 11.30 a.m. by two 21 day "birds", one 19 day,
one 16 day & one 12 day "bird." Initial chill 11.30 at night,

[Text of letter:]

Columbia Barracks

Quemados,

Dec 10th 1900.

My Dear Truby;

Just a line to thank you for the mosquitoes which came safely
 several days ago, (& which proved to be beautiful specimens of
 C. Fasciatus), and, also, to tell you that the theory is alright! Our
 first case came down in Camp (Kissenger) on Saturday night -
 was bitten on 5th at 11.30 a.m. by two 21 day "birds", one 19 day,
one 16 day & one 12 day "bird." Initial chill 11.30 at night,

Saturday; just 84 hours (3 1/2 days) following, with rise of T. to
 100, severe headache and backache, with infected eyes. T. at
 midnight 101 & at 9 a.m. 102.2 &c! [et cetera] The case is a
 beautiful one, and will be seen by the Board of Havana experts,
 to-day, all of whom except Finlay, consider the theory a wild one!

Cooke & CO in infected bedding house are enjoying their
 usual health, but much relieved when told that C. Fasciatus
 had got in his work! Congratulations are now in order -
 Love to my boy -

Sincerely, your friend,

Walter Reed

Historical Background: Major Jefferson Randolph Kean was in the hospital at Columbia Barracks suffering from yellow fever when Walter Reed and James Carroll arrived in Cuba on June 25, 1900. Kean was a good friend of Reed's, and one of the first things Reed did was to visit him. Kean's was the first actual case of yellow fever Reed had ever seen. Kean recovered and resumed his duties as Chief Surgeon, Department of Havana and Pinar del Rio. With his recent illness and position of medical responsibility, Kean had many reasons to be interested in the work of the Board. He encouraged Reed to visit Major General Leonard Wood, Governor-General of Cuba and also a physician, to request his help with financial and command support for further experiments to include human experimentation. They did so on October 12, 1900. Wood immediately agreed. The following day, October 13, 1900, Kean, who was so convinced of the mosquito's role in transmission of disease following the cases of Carroll, patient XY (Private Dean) and Lazear, issued Circular No. 8 in his role as Chief Surgeon, Department of Havana and Pinar del Rio (Fig. 1). This was the first of several orders issuing instructions on the control of mosquitoes, but this one applied only to his department. In late November 1900, Kean was Acting Chief Surgeon, Department of Cuba because the Chief Surgeon, Colonel Valery Havard, was in the U.S. on leave. Camp Lazear had recently opened and by mid-December the Board had produced four additional cases of yellow fever by the bites of "loaded" mosquitoes. Kean drew up this order and was responsible for getting it approved by General Wood.

Jefferson Randolph Kean was a strong supporter of Walter Reed and campaigned unsuccessfully for him to become Surgeon General in 1902. Kean was present at Reed's fateful operation for appendicitis and was charged with selecting his gravesite at Arlington National Cemetery. Later a Brigadier General, he became one of the Army Medical Department's guardians of the legacy of the Yellow Fever Board, preparing many of the official documents responding to request for information about the Board. He spoke at the dedication of the reconstruction of Walter Reed's birthplace in 1927 and wrote the Introduction to Albert E. Truby's book *Memoir of Walter Reed — The Yellow Fever Episode*.

General Orders No. 6: Headquarters Department of Cuba, Havana, December 21, 1900*

GENERAL ORDERS)
NO. 6.)

HEADQUARTERS DEPARTMENT OF CUBA.
Havana, December 21, 1900.

The Chief Surgeon of the Department having reported that it is now well established that malaria, yellow fever and filarial infection are transmitted by the bites of mosquitoes, the following precautions will, upon his recommendation, be taken for the protection of the troops against the bites of these insects:

1. The universal use of mosquito bars in all barracks and especially in all hospitals, and also in field service when practicable.

2. The destruction of the larvae or young mosquitoes, commonly known as "wiggletails" or "wigglers", by the use of petroleum on the water where they breed.

The mosquito does not fly far and seeks shelter when the wind blows; so it is usually the case that each community breeds its own supply of mosquitoes in water barrels, fire buckets, post holes, old cans, cesspools, or undrained puddles.

An application of one ounce of kerosene to each fifteen square feet of water, twice a month, will destroy not only all the young, but the adult females who come to lay their eggs. The water in cisterns or tanks is not affected for drinking or washing purposes by this application if only it is drawn from below and not dipped out.

For pools or puddles of a somewhat permanent character, draining or filling up is the best remedy.

The Medical Department will furnish oil for the purpose above mentioned.

Post commanders will carefully carry out these precautions.

BY COMMAND OF MAJOR GENERAL WOOD.

H. L. SCOTT,
Adjutant General.

* Document courtesy of the National Archives.

Historical Background: Presented below is a portion of a longer letter that Walter Reed wrote to his wife from Cuba on New Year's Eve 1900 (Fig. 1). His obvious love and concern for his family clearly shows through, as does his excitement at the Board's discoveries and his appreciation for the historical significance of their work.

Letter: Walter Reed to Emilie Reed, 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 ^{most} 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! 12 midnight! A thousand and happy new years to my precious, thrice precious wife and daughter! Congratulations to my sweet girls on their good health upon the arrival of the New Century! Hark! there go the 24 buglers all in concert, sounding "Taps" for the old year! How beautiful it floats through the midnight air, and how appropriate! Goodnight my great joys, a thousand sweet dreams of father and dear brother! Kisses & love & love & kisses for my precious, thrice precious girls in these first minutes of the 20th Century!

[Text of letter:]

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 and my assistants to lift the impenetrable veil that has surrounded the causation of this most dreadful pest of humanity and to put it on a rational and 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! 12 midnight! A thousand happy New Years to my precious, thrice precious wife and daughter! Congratulations to my sweet girls on their good health upon the arrival of the new century! Hark! There go the 24 buglers all in concert, sounding "Taps" for the old year! How beautiful it floats through the midnight air and how appropriate! Goodnight my great joys, a thousand sweet dreams of father and dear brother! Kisses and love and love and kisses for my precious girls in these first minutes of the 20th century!

*The original letter courtesy of The Philip S. Hench Walter Reed Yellow Fever Collection, Historical Collections and Services, The Claude Moore Health Sciences Library, University of Virginia.

Historical Background: This second publication of the Board was read by Walter Reed before the Pan-American Medical Congress held in Havana, Cuba, February 6, 1901 and published in the *Journal of the American Medical Association* 36: 431-440 on February 16, 1901. This paper presents five cases of yellow fever produced by the bites of infected mosquitoes, the negative results of the fomite experiments, the one experiment on how a building becomes infected, and four cases produced by subcutaneous injection of blood from acute yellow-fever patients. Based on these 10 cases, they made 11 remarkable conclusions about yellow fever that have stood the test of a century of time. This paper and the discussion that followed its presentation are reprinted in their entirety. The accompanying Editorial (*JAMA* 36: 446-447, 1901), defending the use of human volunteers, is included.

The Etiology of Yellow Fever: An Additional Note

Walter Reed, MD, Surgeon, United States Army, James Carroll, MD, and Aristides Agramonte, MD, Acting Assistant-Surgeons, United States Army

At the Twenty-eighth Annual Meeting of the American Public Health Association,¹ held in Indianapolis, Ind., Oct. 22-26, 1900, we presented, in the form of a preliminary note, the results of our bacteriologic study of yellow fever, based on cultures taken from the blood in eighteen cases, at various stages of the disease, as well as on those which we had made from the blood and organs of eleven yellow fever cadavers. We also recorded the results obtained from the inoculation of eleven non-immune individuals by means of the bite of mosquitoes (*Culex fasciatus*, Fabr.) that had previously fed on the blood of patients sick with yellow fever. We were able to report two positive results, in which the attack of yellow fever followed the bite of a mosquito within the usual period of incubation of this disease.

In one of these cases all other sources of infection could be positively excluded. From our several observations we drew the following conclusions. 1. *Bacillus icteroides* (Sanarelli) stands in no causative relation to yellow fever, but, when present, should be considered as a secondary invader in this disease. 2. The mosquito serves as the intermediate host for the parasite of yellow fever. Since the publication of our preliminary note, we have continued our investigations, especially as regards the means by which yellow fever is propagated from individual to individual, and as to the manner in which houses become infected with the contagium of this disease. The results already obtained are so positive and striking that, with the permission of Surgeon-General Sternberg, we have concluded to present to this Congress an additional note, in which we will record these later observations. We desire to here express our sincere thanks to the Military Governor of the Island of Cuba, Major General Leonard Wood, U.S.V., without whose approval and assistance these observations could not have been carried out.

In order to exercise perfect control over the movements of those individuals who were to be subjected to experimentation, and to avoid any other possible source of infection, a location was selected in an open and uncultivated field, about 1 mile from the town of Quemados, Cuba. Here an experimental sanitary station was established under the complete control of the senior member of this Board. This station was named Camp Lazear, in honor of our late colleague, Dr. Jesse W. Lazear, Acting Assistant-Surgeon, U.S.A., who died of yellow fever, while courageously investigating the causation of this disease. The site selected was very well drained, freely exposed to sunlight and winds, and, from every point of view, satisfactory for the purposes intended.

The personnel of this camp consisted of two medical officers, Dr. Roger P. Ames, Acting Assistant-Surgeon, U.S.A., an immune, in immediate charge; Dr. R. P. Cooke, Acting Assistant-Surgeon, U.S.A., non-immune; one acting hospital steward, an immune; nine privates of the hospital corps, one of whom was immune, and one immune ambulance driver.

For the quartering of this detachment and of such non-immune individuals as should be received for experimentation, hospital tents, properly floored, were provided. These were placed at a distance of about twenty feet from each other, and were numbered 1 to 7 respectively.

Camp Lazear was established Nov. 20, 1900, and from this date was strictly quarantined, no one being permitted to leave or enter camp except the three immune members of the detachment and the members of the Board. Supplies were drawn chiefly from Columbia Barracks, and for purpose of conveyance under the control of an immune acting hospital steward, and having an immune driver, was used.

A few Spanish immigrants recently arrived at the Port of Havana, were received at Camp Lazear, from time to time, while these observations were being carried out. A non-immune person, having once left this camp, was not permitted to return to it under any circumstances whatever.

The temperature and pulse of all non-immune residents were carefully recorded three times a day. Under these circumstances any infected individual entering the camp could be promptly detected and removed. As a matter of fact only two persons not the subject of experimentation, developed any rise of temperature; one, a Spanish immigrant, with probably commencing pulmonary tuberculosis, who was discharged at the end of three days; and the other, a Spanish immigrant, who developed a temperature of 102.6 F. on the afternoon of his fourth day in camp. He was at once removed with his entire bedding and baggage and placed in the receiving ward at Columbia Barracks. His fever, which was marked by daily intermissions for three days, subsided upon the administration of cathartics and enemata. His attack was considered to be due to intestinal irritation. He was not permitted, however, to return to the camp.

No non-immune resident was subjected to inoculation who had not passed in this camp the full period of incubation of yellow fever, with one exception, to be hereinafter mentioned.

Observations

Having thus sufficiently indicated the environment of Camp Lazear and the conditions under which its residents lived, we will now proceed to a narration of the observations thus far made at this experimental station. At the time these inoculations were begun, the several tents were occupied as follows: Tent No. 1 by 1 immune and 1 non-immune; No. 2 by 1 immune and 2 non-immunes; No. 3 by 2 immunes; No. 4 by 3 non-immunes; No. 5 by 3 non-immunes; No. 6 by 2 non-immunes; and No. 7 by 1 non-immune.

For the purpose of experimentation subjects were selected as follows: from Tent No. 2, 2 non-immunes, and from Tent No. 5, 3 non-immunes. Later, 1 non-immune in Tent No. 6 was also designated for inoculation.

Case 1

Private John R. Kissinger, Hospital Corps, U.S.A., aged 23, a non-immune, occupant of Tent No. 2, with his full consent, was bitten at 10.30 a.m., November 20, 1900, by a mosquito—*C. fasciatus*—that had bitten a severe case of yellow fever on the fifth day, eleven days previously; another severe case, on the third day, six days before, and a third severe one on the third day, three days before. As Kissinger had not absented himself from Columbia Barracks for a period of more than thirty days, it was considered safe to inoculate him without waiting for his period of incubation to pass.

November 23, 1900, Kissinger was again bitten by the same mosquito. The result of both inoculations was negative. The mosquito, therefore, was incapable of conveying any infection on the eleventh or fourteenth day after it had bitten a severe case of yellow fever on the third day of the disease. This insect had been kept at ordinary room temperature and died November 26, 1900.

December 5, 1900, at 2 p.m., twelve days after the last inoculation Kissinger was again bitten by five mosquitoes—*C. fasciatus*—two of which had bitten fatal cases of yellow fever, on the second day, fifteen days before; one a severe case on the second day, nineteen days previously, and two a mild case on the third day, twenty-one days before.

The record of temperature and pulse, taken every three hours, following this inoculation, showed that the subject remained in his usual state of health during the following 3 days, except that on December 8, on the third day, Kissinger had slight vertigo, upon rising, which soon passed away. At 4.30 p.m. — commencement of fourth day — he complained of frontal headache; otherwise he felt well and partook of supper with appetite; at 9 p.m., temperature was 98.4 F., pulse 90; at 11.30 p.m., he awoke with a chill, his temperature 100 F., pulse 90; he complained of severe frontal headache and backache, his eyes were injected and his face suffused. December 9 at 3 a.m. his temperature was 102 F., pulse 102; he had violent headache and backache with nausea and vomiting. He was then removed to the yellow fever wards. His subsequent history was that of a case yellow fever at moderate severity. Albumin appeared in the urine on the fourth day, increased to one-fifth by volume, the sixth day and disappeared on December 22. Granular casts were present in considerable numbers from the fourth to the eighth day. The conjunctive were jaundiced on the third day. The diagnosis of yellow fever in this case was made by Drs. Juan Guit  ras, Carlos

Finlay, W.C. Gorgas, and A. Diaz Albertini, the board of yellow fever experts of the city of Habana, who saw the patient on several occasions during his illness. (See Chart I.) The period of incubation in this case was 3 days, 9½ hours.

Case 2

John J. Moran, aged 24, an American, non-immune occupant of Tent No. 2, with his full consent, was bitten at 10 a.m., November 26, 1900, by a mosquito — *C. fasciatus* — which twelve days before had bitten a case of yellow fever of moderate severity, on the third day of the disease. This insect had also bitten a well-marked case of yellow fever—second day—ten days previously.

November 29, at 2.20 p.m., Moran was again bitten by the same mosquito. The result of both of these inoculations negative. This insect was, therefore, incapable of conveying infection fifteen days after having bitten a case of yellow fever of moderate severity on the third day, and thirteen days after it had bitten a well-marked case of this disease on the second. This mosquito had been kept at room temperature. Moran's case will be again referred to when we come to speak of infection of a building by means of contaminated mosquitoes.

Case 3

A Spanish immigrant, aged 26, a non-immune occupant of Tent No. 5, with his full consent, was bitten at 4 p.m., December 8, 1900, by four mosquitoes — *C. fasciatus* — which had been contaminated as follows: one by biting a fatal case yellow fever, on the third day, seventeen days before; one a severe one, on the third day, eighteen days before; one a severe case, on the second day, twenty-two days before, and one a case of moderate severity, on the third day, twenty-four days previously.

The record of temperature and pulse, taken every three hours after the inoculation, shows no rise of temperature above 99 F. until 6 p.m., December 13, on the sixth day, when 99.4 F. is recorded; pulse 68. The subject, who was of a very lively disposition, retained his usual spirits until noon on the 13th, although he complained of slight frontal headache on the 11th and 12th. He took to his bed at noon of the 13th, the fifth day, complaining of increased frontal headache and a sense of fatigue. At 9 p.m., his temperature was 98.2 F., pulse 62.

December 14, at 6 a.m., temperature was 98 F., pulse 72, and he still complained of frontal headache and general malaise. Profuse epistaxis occurred at 7.45 a.m.; at 9 a.m. temperature was 99.6 F., pulse 80, at 1.15 p.m., temperature was 100 F., pulse 80, and he had complained of a sense of chilliness, with frontal headache increased, and slight pain in the back, arms and legs; at 3 p.m., temperature was 100 F, pulse 80; at 4.15 p.m., temperature 100.7 F., pulse 68; his face flushed and eyes congested. He was removed to the yellow fever wards. A trace of albumin was found in the urine passed at 3:30 p.m. December 15; a few hyaline casts were present. He was seen at this time by the Havana board of experts and the diagnosis of mild yellow fever confirmed. (See Chart No. II.)

The period of incubation in this case was four days and twenty hours, counting from the time of inoculation to the hour when the patient took to his bed; if reckoned to the onset of fever, it was 5 days and 17 hours.

Case 4

A Spanish immigrant, aged 27, a non-immune occupant of Tent No. 5, with his full consent, was bitten at 10 a.m., November 26, 1900, by a mosquito — *C. fasciatus* — which had bitten a severe case of yellow fever, on the second day, ten days before. Three days later, November 29, he was again bitten by the same insect. December 2, after an interval of three days, he was again bitten by the same insect, and also by a second mosquito — *C. fasciatus* — which, twelve days before, had been contaminated by biting a fatal case of yellow fever on the third day. No unfavorable effects followed any of these attempted inoculations. The first-mentioned mosquito, therefore, was incapable of conveying any infection on the seventeenth day after biting a severe case of yellow fever on the second day; the other also failed to infect on the twelfth day after biting a fatal case of yellow fever on the third day. Both of these mosquitoes had been kept at ordinary room temperature.

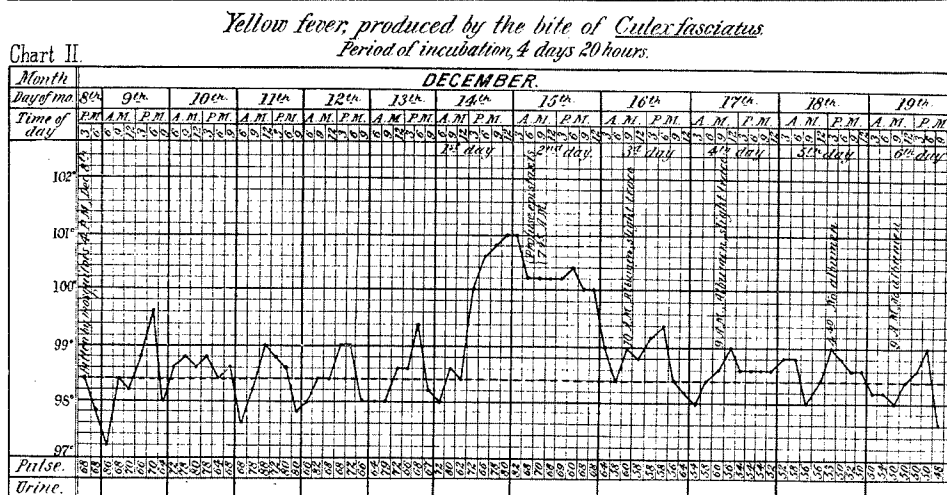
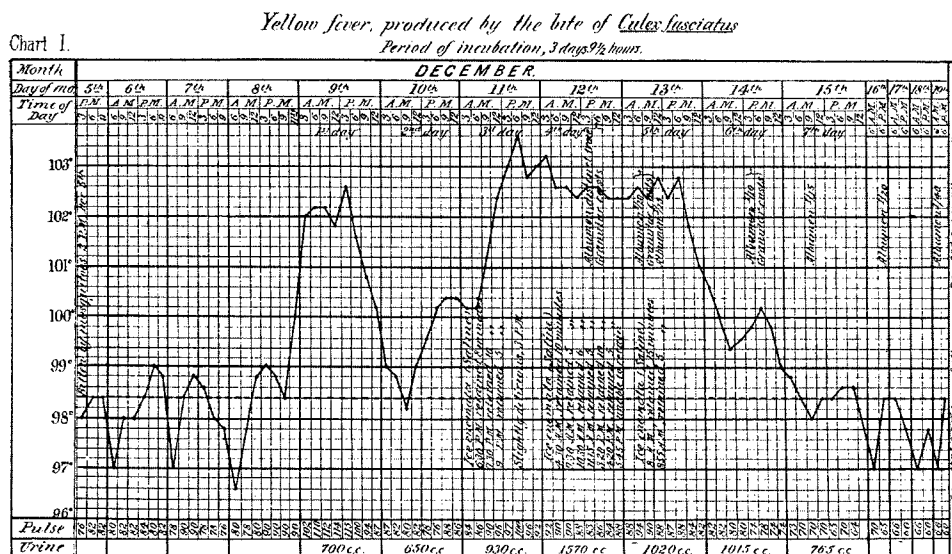
December 9, after an interval of seven days, the subject was again bitten, at 10.30 a.m., by one mosquito — *C. fasciatus* — which had been infected nineteen days before by biting a fatal case of yellow fever on the second day of the disease. He remained in his usual health until 9 a.m., December 12, the third

day, when he complained of frontal headache; his temperature was 98.8 F., pulse 96. This headache continued during the entire day. At 6 p.m., temperature was 99 F., pulse 94; at 9 p.m., temperature 99 F., pulse 84; at 9.30 p.m., temperature 99.4 F., pulse 82. Severe headache and backache was complained of; his eyes were injected and his face suffused. The following morning he was sent to the yellow fever wards. Urine passed at 4.20 p.m., December 15, the third day, gave a distinct trace of albumin. Many hyaline casts were present on the same date. The conjunctiva were jaundiced on the third day. The patient was seen by the board of experts on December 14, and the diagnosis of yellow fever made. (See Chart No. III.)

The period of incubation in this case was 3 days, 11½ hours.

Case 5

A Spanish immigrant, aged 26, a non-immune occupant of Tent No. 5, with his full consent, was bitten at 10 a.m., November 26, 1900, by a mosquito — *C. fasciatus* — that had bitten a well-marked case of yellow fever, on the third day, twelve days before. November 29 he was again bitten by the same insect. December 2 he was for the third time bitten by two mosquitoes — *C. fasciatus* — both of which had bitten a well-marked case of



yellow fever, on the third day, eighteen days before. As no bad results followed any of these inoculations, it follows that these mosquitoes were incapable of conveying any infection eighteen days after they had bitten a well-marked case of yellow fever on the third day. Both of these insects had been kept at room temperature.

December 11, after an interval of nine days, the subject was again, at 4:30 p.m., bitten by the same mosquitoes, four in number, that had been applied to Case 3, three days prior to this time, with positive results.

The record of temperature and pulse, taken every three hours following the inoculation, showed no change till December 13, the second day, at 9 a.m., when the temperature was 99 F., and the pulse 78. From this hour till 6 p.m. the temperature varied from 99.2 to 99.6 F. The subject complained of frontal headache, slight in degree, during the entire day. At 9 p.m. his temperature was 98.4 F., pulse 62.

December 14, the third day, he complained of slight frontal headache during the entire day, and was indisposed to exertion. From 6 a.m. to 6 p.m. the temperature averaged 99.2 F., and the pulse varied from 64 to 90; at 9 p.m. it was 98.4 F., the pulse 78. December 15, the fourth day, at 6 a.m., temperature was 98.2 F., pulse 78. He still had frontal headache. At 9 a.m., temperature was 99.2 F., pulse 80; at 12, noon, the former was 99.2 F., the pulse 74. The subject now went to bed, complaining of headache and pains throughout the body. At 2 p.m., the temperature was 100 F., the pulse 80; eyes much congested; face

flushed. At 6 p.m. his temperature had risen to 102 F., and the pulse to 90. He was then transferred to the yellow fever wards. Albumin appeared in the urine at 7:30 a.m., December 17. Bleeding from the gums and roof of the mouth occurred on the sixth and seventh days of his illness.

This case was examined by the board of experts on the 16th and 19th, and the diagnosis of yellow fever made.

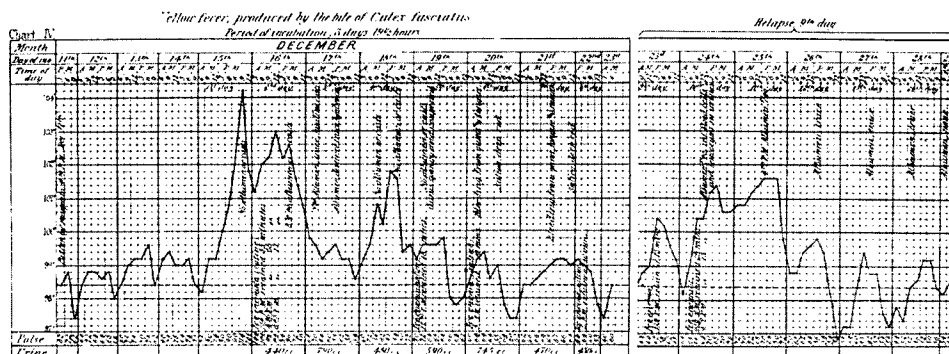
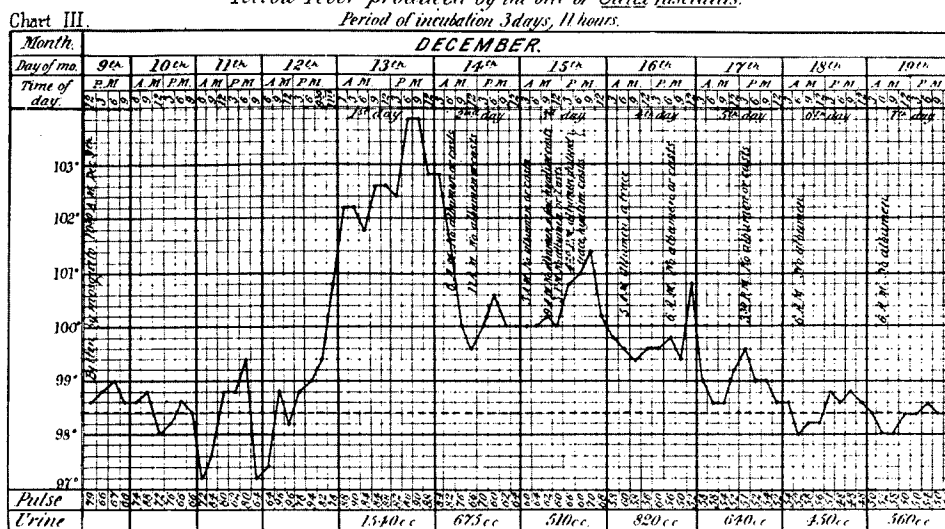
Albumin disappeared on the sixth day, the temperature falling to normal on this date, and remaining near this point till December 23, the ninth day of sickness, when a relapse occurred, attended with bleeding from the gums on December 24 and 25, with the appearance of red blood cells and pus cells in the urine in moderate numbers. Fever subsided on December 26, and the urine became normal on December 29. (See Chart No. IV.)

The period of incubation in this case, if reckoned from the time of inoculation to the hour when the patient took to his bed was 3 days, 19½ hours.

The four patients whose histories we have given above were also examined by a number of physicians of Habana, among whom we may mention Dr. Bango, of "La Covadonga," Dr. Sanchez, of "La Benéfica," and Dr. Moas, of "La Purissima Concepcion," by all of whom the diagnosis of yellow fever was confirmed. Let us now rapidly review the circumstances attending these cases of experimental yellow fever, in order to emphasize certain points of interest and importance in connection with occurrence. (We omit any reference to the clinical histories.)

Yellow fever produced by the bite of *Culex fasciatus*.

Period of incubation 3 days, 11 hours.



It should be borne in mind that at the time when these inoculations were begun, there were only 12 non-immune residents at Camp Lazear, and that 5 of these were selected for experiment, viz., 2 in Tent No. 2, and 3 in Tent No. 5. Of these we succeeded in infecting 4, viz., 1 in Tent No. 2 and 3 in Tent No. 5, each of whom developed an attack of yellow fever within the period of incubation of this disease. The one negative result, therefore, was in Case 2-Moran-inoculated with a mosquito on the fifteenth day after the insect had bitten a case of yellow fever on the third day. Since this mosquito failed to infect Case 4, three days after it had bitten Moran, it follows that the result could not have been otherwise negative in the latter case. We now know, as the result our observations, that in the case of an insect kept at room temperature during the cool weather of November, fifteen or even eighteen days would, in all probability, be too short a time to render it capable of producing the disease.

As bearing upon the source of infection, we invite attention to the period of time during which the subjects had been kept under rigid quarantine, prior to successful inoculation, which was as follows: Case 1, fifteen days; Case 3, nine days; Case 4, nineteen days; Case 5, twenty-one days. We further desire to emphasize the fact that this epidemic of yellow fever, which affected 33.33 per cent of the non-immune residents of Camp Lazear, did not concern the 7 non-immunes occupying Tents No. 1, 4, 6, and 7, *but was strictly limited to those individuals who had been bitten by contaminated mosquitoes.*

Nothing could point more forcibly to the source of this infection than the order of the occurrence of events at this camp. The precision with which the infection of the individual followed the bite of the mosquito left nothing to be desired in order to fulfill the requirements of a scientific experiment.

The epidemic having ceased on Dec. 15, 1900 no other case of yellow fever occurred in this camp until we again began to expose individuals to inoculation. Thus fifteen days later we made the following observation.

Case 6

A Spanish immigrant, aged 27, a non-immune occupant of Tent No. 6, with his full consent, was bitten at 11 a.m., December 30, 1900 by four mosquitoes — *C. fasciatus* — that had been contaminated seventeen days previously by biting a mild case of yellow fever on the first day of the disease (Case 4). These insects had been kept at a temperature of 82 F.

The subject remained in his normal condition until the evening of January 2, 1901, the third day, when he complained of frontal headache. At 6 p.m., his temperature was 99 F., pulse 64. He slept well, but still complained of headache on the following morning, January 3. He partook sparingly of breakfast, and afterward lay on his bed, being disinclined to exert himself. At 9 a.m., the temperature was 99 F., the pulse 96; at 10:30 a.m., temperature 100 F., pulse 80. A sense of chilliness and sharp frontal headache was complained of, and at 3 p.m. his temperature was 100.8 F., his pulse 89, and his eyes were congested and face flushed. He was removed to the yellow fever wards. A specimen of urine passed at midnight, January 4, contained a distinct trace of albumin. Slight bleeding from the gums occurred on the fifth and sixth days. The patient was seen by the board of experts on the second and seventh days of his attack, and the diagnosis of yellow fever confirmed. (See Chart No. V.)

The period of incubation in this case was three days, 22½ hours. The subject had remained in strict quarantine for twenty-two days preceding his inoculation.

In considering the character of the attacks and the course of the disease in these five cases of experimental yellow fever, it must be borne in mind that these infected individuals were all young men, in good general physical condition, and placed amid excellent hygienic surroundings. Further, it must not be forgotten that, upon the earliest manifestation of an approaching infection, they were each and all put to bed at once, and were even carried to the yellow fever wards while occupying the same bed. In other words, these men were kept at absolute rest from the first inception of the disease. Just what bearing this may have had on the subsequent course of the fever, we cannot say, but since so much stress is laid on absolute rest of the patient by those having most experience in the treatment of yellow fever, the influence of this enforced rest, in our cases, upon the subsequent course of the attack, was doubtless of much importance. We reserve a consideration of the clinical side of these cases for a future report.

In our opinion the experiments above described conclusively demonstrate that an attack of yellow fever may be readily induced in the healthy subject by the bite of mosquitoes — *C. fasciatus* — which have been previously contaminated by being fed with the blood of those sick with yellow fever, provided the insects are kept for a sufficient length of time after contamination before being applied to the person to be infected.

Our observations do not confirm Finlay's statement that the bite of the mosquito may confer an abortive attack of yellow fever, when applied to the healthy subject two to six days after it has bitten a yellow fever patient. We have always failed to induce an attack, even of the mildest description, when we have used mosquitoes within less than twelve days from the time of contamination, although the insects were constantly kept at summer temperature. We could cite instances where we have applied mosquitoes at intervals of two, three, four, five, six, nine, and eleven days following the contamination of the insect with the blood of well-marked cases of yellow fever, early in the disease, without any effect whatever being produced by the bite. Thus in one case no result followed the bite of fourteen mosquitoes which four days previously had been contaminated by biting a case of yellow fever on the first day. Again, seven days later, or eleven days after contamination, the surviving seven of these insects failed to infect an individual. On the seventeenth day after contamination, however, the bite of four of these mosquitoes — all that remained of the original fourteen — was promptly followed by an attack of yellow fever in the same individual. These insects had been kept, during the whole of this time, at an average temperature of 82 F.

Our observations would seem to indicate that after the parasite has been taken into the mosquito's stomach, a certain number of days must elapse before the insect is capable of re-conveying it to man. This period doubtless represents the time required for the parasite to pass from the insect's stomach to its salivary glands, and would appear to be about twelve days in summer weather, and most probably about eighteen or more days during the cooler winter months. It follows, also, that our observations do not confirm Finlay's opinion that the bite of the contaminated mosquito may confer immunity against a subse-

quent attack of yellow fever. In our experience, an individual may be bitten on three or more occasions by contaminated mosquitoes without manifesting any symptoms of disturbance to health, and yet promptly sicken with yellow fever within a few days after being bitten by an insect capable of conveying the infection.

Acquirement of the Disease

Having shown that yellow fever can be conveyed by the bite of an infected mosquito, it remains to inquire, whether this disease can be acquired in any other manner. It has seemed to us that yellow fever, like the several types of malarial fever, might be induced by the injection of blood taken from the general circulation of a patient suffering with this disease. Accordingly we have subjected four individuals to this method of infection, with one negative and three positive results. Reserving the detailed description of these cases to a subsequent occasion, we may state that in one of the positive cases an attack of pronounced yellow fever followed the subcutaneous injection of 2 c.c. of blood taken from a vein, bend of the elbow, on the first day of the disease, the period of incubation being three days and twenty-two hours; in the second case, 1.5 c.c. of blood, taken on the first day of the disease, and injected in the same manner brought about an attack within two days and twelve hours; while in our third case, the injection of 0.5 c.c. of blood taken on the second day of the disease, produced an attack at the end of forty-one hours.

In the case mentioned as negative to the blood injection, the subsequent inoculation of this individual with mosquitoes already proved to be capable of conveying the disease, also resulted negatively. We think, therefore that this particular individual, a Spanish immigrant, may be considered as one who probably possesses a natural immunity to yellow fever.

It is important to note that in the three cases in which the injection of the blood brought about an attack of yellow fever, careful cultures from the same blood, taken immediately after injection, failed to show the presence of Sanarelli's bacillus. [Original footnote] A fourth case of yellow fever, severe in type, has been produced, by the subcutaneous injection of 1 c.c. of blood taken from the general circulation on the second day of the disease, the period of incubation being three days and one hour. The patient from whom the blood was obtained was an experimental case which was in turn produced the injection of blood-0.5 c.c.-derived from a non-experimental case of fatal yellow fever. As "controls," Cases 1, 4, 6, and 7 of this report were also injected subcutaneously with 1 c.c. of the same blood without manifesting any symptoms whatever. The blood which produced the fourth case of yellow fever, when transferred at the same time to bouillon tubes in considerable quantities, gave no growth whatever.)

Our observations, therefore, show that the parasite of yellow fever is present in the general and capillary circulation, at least during the early stages of this disease and that the latter may be conveyed, like the malaria parasite, either by means of the bite of the mosquito, or by the injection of blood taken from the general circulation.

Can Yellow Fever Be Propagated in Any Other Way?

We believe that the general consensus of opinion of both the medical profession and the laity is strongly in favor of the conveyance of yellow fever by fomites. The origin of epidemics, devastating in their course, has been frequently attributed to the unpacking of trunks and boxes that contained supposedly infected clothing; and hence the efforts of health authorities, both state and national, are being constantly directed to the thorough disinfection of all clothing and bedding shipped from ports where yellow fever prevails. To such extremes have efforts at disinfection been carried, in order to prevent the importation of this disease into the United States, that, during the epidemic season, all articles of personal apparel and bedding have been subjected to disinfection, sometimes both at the port of departure and at the port of arrival; and this has been done whether the articles have previously been contaminated by contact with yellow fever patients or not. The mere fact that the individual has resided, even for a day, in a city where yellow fever is present, has been sufficient cause to subject his baggage to rigid disinfection by the sanitary authorities.

To determine, therefore, whether clothing and bedding, which have been contaminated by contact with yellow fever patients and their discharges, can convey this disease is a matter of the utmost importance. Although the literature contains many references to the failure of such contaminated articles to cause the disease, we have considered it advisable to test, by actual experiment on non-immune human beings, the theory of the conveyance of yellow fever by fomites, since we know of no other way in which this question can ever be finally determined.

For this purpose there was erected at Camp Lazear a small frame house consisting of one room 14×20 feet, and known as "Building No. 1," or the "Infected Clothing and Bedding Building." The cubic capacity of this house was 2800 feet. It was tightly ceiled within with "tongue and grooved" boards, and was well battened on the outside. It faced to the south and was provided with two small windows, each 26×34 inches in size. These windows were both placed on the south side of the building, the purpose being to prevent, as much as possible, any thorough circulation of the air within the house. They were closed by permanent wire screens of 0.5 mm mesh. In addition sliding glass sash were provided within and heavy wooden shutters without; the latter intended to prevent the entrance of sunlight into the building, as it was not deemed desirable that the disinfecting qualities of sunlight, direct or diffused, should at any time be exerted on the articles of clothing contained within this room. Entrance was effected through a small vestibule, 3×5 feet, also placed on the southern side of the house. This vestibule was protected without by a solid door and was divided in its middle by a wire screen door, swung on spring hinges. The inner entrance was also closed by a second wire screen door. In this way the passage of mosquitoes into this room was effectually excluded. During the day, and until after sunset, the house was kept securely closed, while by means of a suitable heating apparatus the temperature was raised to 92 to 95 F. Precaution was taken at the same time to maintain a sufficient humidity of the atmosphere. The average temperature of this house was thus kept at 76.2 F. for a period of 63 days.

Nov. 30, 1900, the building now being ready for occupancy, three large boxes filled with sheets, pillowslips, blankets, etc.,

contaminated by contact with cases of yellow fever and their discharges were received and placed therein. The majority of the articles had been taken from the beds of patients sick with yellow fever at Las Animas Hospital, Habana, or at Columbia Barracks. Many of them had been purposely soiled with a liberal quantity of black vomit, urine, and fecal matter. A dirty "comfortable" and much-soiled pair of blankets, removed from the bed of a patient sick with yellow fever in the town of Quemados, were contained in one of those boxes. The same day, at 6 p.m., Dr. R.P. Cooke, Acting Assistant-Surgeon, U.S.A., and two privates of the hospital corps, all non-immune young Americans entered this building and deliberately unpacked these boxes, which had been tightly closed and locked for a period of two weeks. They were careful at the same time to give each article a thorough handling and shaking in order to disseminate through the air of the room the specific agent of yellow fever, if contained in these fomites. These soiled sheets, pillowcases, and blankets were used in preparing the beds in which the members of the hospital corps slept. Various soiled articles were hung around the room and placed about the bed occupied by Dr. Cooke.

From this date until Dec. 19, 1900, a series of twenty days, this room was occupied each night by these three non-immunes. Each morning the various soiled articles were carefully packed in the aforesaid boxes, and at night again unpacked and distributed about the room. During the day the residents of this house were permitted to occupy a tent pitched in the immediate vicinity, but were kept in strict quarantine.

December 12, a fourth box of clothing and bedding was received from Las Animas Hospital. These articles, had been used on the beds of yellow fever patients, but in addition had been purposely soiled with the bloody stool of a fatal case of this disease. As this box had been packed for a number of days, when opened and unpacked by Dr. Cooke and his assistants, on December 12, the odor was so offensive as to compel them to retreat from the house. They pluckily returned, however, within a short time and spent the night as usual.

December 19 these three non-immunes were placed in quarantine for five days and then given the liberty of the camp. All had remained in perfect health, notwithstanding their stay of twenty nights amid such unwholesome surroundings.

During the week, December 20-27, the following articles were also placed in this house, viz.: pajamas suits, 1; undershirts, 2; night-shirts, 4; pillow-slips, 4; sheets, 6; blankets, 5; pillows, 2; mattresses, 1. These articles had been removed from the persons and beds of four patients sick with yellow fever and were very much soiled, as any change of clothing or bed-linen during their attacks had been purposely avoided, the object being to obtain articles as thoroughly contaminated as possible.

From Dec. 21, 1900, till Jan. 10, 1901, this building was again occupied by two non-immune young Americans, under the same conditions as the preceding occupants, except that these men slept every night in the very garments worn by yellow fever patients throughout their entire attacks, besides making use exclusively of their much-soiled pillow-slips, sheets, and blankets. At the end of twenty-one nights of such intimate contact with fomites, they also went into quarantine, from which they were released five days later in perfect health.

From January 11 till January 31, a period of twenty days, "Building No. 1" continued to be occupied by two other non-

immune Americans, who, like those who preceded them, have slept every night in the beds formerly occupied by yellow fever patients and in the nightshirt used by these patients throughout the attack, without change. In addition, during the last fourteen nights of their occupancy of this house they have slept, each night, with their pillows covered with towels that had been thoroughly soiled with the blood drawn from both the general and capillary circulation, on the first day of the disease, in the case of a well-marked attack of yellow fever. Notwithstanding this trying ordeal, these men have continued to remain in perfect health.

The attempt which we have therefore made to infect "Building No. 1," and its seven non-immune occupants, during a period of sixty-three days, has proved an absolute failure. We think we cannot do better here than to quote from the classic work of La Roche.² This author says: In relation to the yellow fever, we find so many instances establishing the fact of the nontransmissibility of the disease through the agency of articles of the kind mentioned, and of merchandise generally, that we cannot but discredit the accounts of a contrary character assigned in medical writings, and still more to those presented on the strength of popular report solely. For if in a large number of well authenticated cases, such articles have been handled and used with perfect impunity — and that, too, often under circumstances best calculated to insure the effect in question — we have every reason to conclude, that a contrary result will not be obtained in other instances of a similar kind; and that consequently the effect said to have been produced by exposure to those articles, must — unless established beyond the possibility of doubt — be referred to some other agency.

The question here naturally arises: How does a house become infected with yellow fever? This we have attempted to solve by the erection at Camp Lazear of a second house, known as "Building No. 2," or the "Infected Mosquito Building." This was in all respects similar to "Building No. 1," except that the door and windows were placed on opposite sides of the building so as to give through-and-through ventilation. It was divided, also, by a wire-screen partition, extending from floor to ceiling, into two rooms, 12×14 feet and 8×14 feet respectively. Whereas, all articles admitted to "Building No. 1" had been soiled by contact with yellow fever patients, all articles admitted to "Building No. 2" were first carefully disinfected by steam before being placed therein.

On Dec. 21, 1900, at 11.45 a.m., there were set free in the larger room of this building 15 mosquitoes — *C. fasciatus* — which had previously been contaminated by biting yellow fever patients, as follows: 1, a severe case, on the second day, Nov. 27, 1900, twenty-four days; 3, a well-marked case, on the first day, Dec. 9, 1900, twelve days; 4, a mild case, on the first day, Dec. 13, 1900, eight days; 7, a well-marked case, on the first day, Dec. 16, 1900, five days-total, 15.

Only one of these insects was considered capable of conveying the infection, viz., the mosquito that had bitten a severe case twenty-four days before; while three others — the twelve-day insects — had possibly reached the dangerous stage, as they had been kept at an average temperature of 82 F.

At 12, noon, of the same day, John J. Moran — already referred to as Case 2 in this report — a non-immune American, entered the room where the mosquitoes had been freed, and

remained thirty minutes. During this time he was bitten about the face and hands by several insects. At 4.30 p.m., the same day, he again entered and remained twenty minutes, and was again bitten. The following day, at 4.30 p.m., he, for the third time, entered the room, and was again bitten.

Case 7

On December 25, 1900, at 6 a.m., the fourth day, Moran complained of slight dizziness and frontal headache. At 11 a.m. he went to bed, complaining of increased headache and malaise, with a temperature of 99.6 F., pulse 88; at noon the temperature was 100.4 F., the pulse 98; at 1 p.m., 101.2 F., the pulse 96, and his eyes were much injected and face suffused. He was removed to the yellow fever wards. He was seen on several occasions by the board of experts and the diagnosis of yellow fever confirmed. (See Chart No. VI).

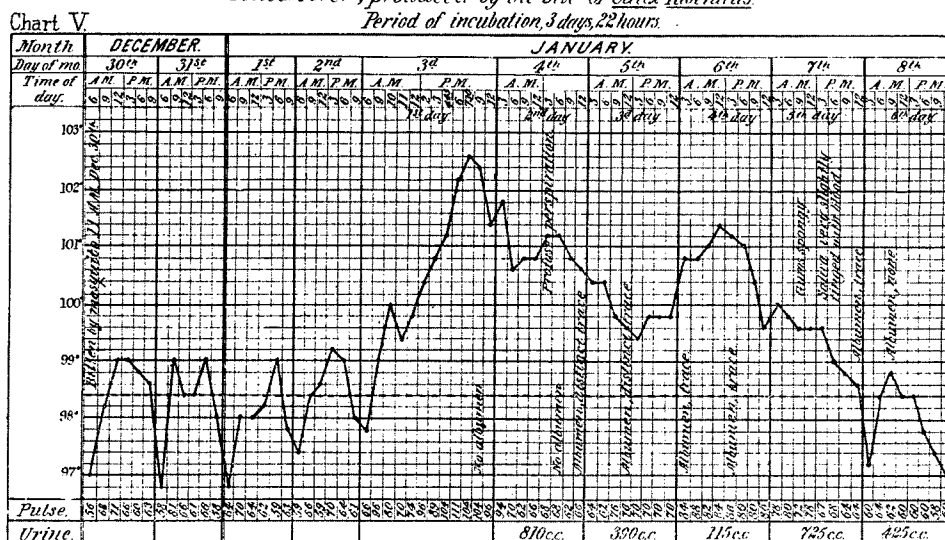
The period of incubation in this case, dating from the first visit to "Building No. 2," was three days and twenty-three hours. If

reckoned from his last visit it was two days and eighteen hours. There was no other possible source for his infection, as he had been strictly quarantined at Camp Lazear for a period of the thirty-two days prior to his exposure in the mosquito building.

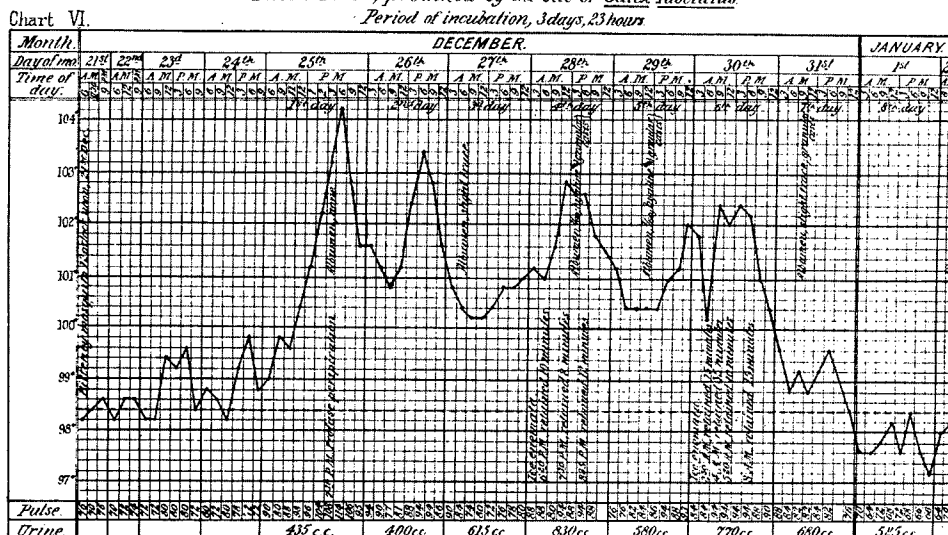
During each of Moran's visits, two non-immunes remained in this same building, only protected from the mosquitoes by the wire-screen partition. From Dec. 21, 1900, till Jan. 8, 1901, inclusive — eighteen nights — these non-immunes have slept in this house, only protected by the wire screen partition. These men have remained in perfect health to the present time.

December 28, after an interval of seven days, this house was again entered by a non-immune American, who remained twenty-five minutes. The subject was bitten by only one insect. The following day he again entered and remained fifteen minutes, and was again bitten by one mosquito. The result of these two visits was entirely negative. As the mortality among the insects in this room, from some unknown cause, had been surprisingly large, it is possible that the subject was bitten by insects not more than thirteen days old, in which case they would probably

Yellow fever, produced by the bite of Culex fasciatus
Period of incubation, 3 days, 22 hours.



Yellow fever, produced by the bite of Culex fasciatus
Period of incubation, 3 days, 23 hours.



not infect, since they had been kept for only five days at a temperature of 82 F., and for eight days at the mean temperature of the room, 78 F.

Be this as it may, nothing can be more striking or instructive as bearing upon the cause of house infection in yellow fever, than when we contrast the results obtained in our attempts to infect Buildings No. 1 and No. 2; for whereas, in the former all of seven non-immunes escaped the infection, although exposed to the most intimate contact with the fomites for an average period of twenty-one nights each; in the latter, an exposure, reckoned by as many minutes, was quite sufficient to give an attack of yellow fever to one out of two persons who entered the building — 50 per cent.

Thus at Camp Lazear, of 7 non-immunes whom we attempted to infect by means of the bites of contaminated mosquitoes, we have succeeded in conveying the disease to 6, or 85.71 per cent. On the other hand, 7 non-immunes whom we tried to infect by means of fomites, under particularly favorable circumstances, we did not succeed in a single instance. Out of a total of 18 non-immunes whom we have inoculated with contaminated mosquitoes, since we began this line of investigation, 8, or 44.4 per cent., have contracted yellow fever. If we exclude those individuals bitten by mosquitoes that had been kept less than twelve days after contamination, and which were, therefore, probably incapable of conveying the disease, we have to record eight positive and two negative results — 80 per cent.

Conclusions

(1) The mosquito — *C. fasciatus* — serves as the intermediate host for the parasite of yellow fever.

(2) Yellow fever is transmitted to the non-immune individual by means of the bite of the mosquito that has previously fed on the blood of those sick with this disease.

(3) An interval of about twelve days or more after contamination appears to be necessary before the mosquito is capable of conveying the infection.

(4) The bite of the mosquito at an earlier period after contamination does not appear to confer any immunity against a subsequent attack.

(5) Yellow fever can also be experimentally produced by the subcutaneous injection of blood taken from the general circulation during the first and second days of this disease.

(6) An attack of yellow fever, produced by the bite of the mosquito, confers immunity against the subsequent injection of the blood of an individual suffering from the non-experimental form of this disease.

(7) The period of incubation in thirteen cases of experimental yellow fever has varied from forty-one hours to five days and seventeen hours.

(8) 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.

(9) 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.

(10) The spread of yellow fever can be most effectually controlled by measures directed to the destruction of mosquitoes and the protection of the sick against the bites of these insects.

(11) While the mode of propagation of yellow fever has now been definitely determined, the specific cause of this disease remains to be discovered.

Discussion

DR. LOUIS PERNA, Cienfuegos, Cuba, in opening the discussion, said that it is sophism to believe that post hoc, ergo propter hoc; that is to say, that, as Carmona, Freire, Sanraelli, and others have fallen to this error, we must not be too precipitate in accepting the results of statistics. The studies made of mosquitoes are very old. A French physician, who died about 1850, expressed the opinion that malaria, yellow fever, and cholera were propagated by mosquitoes. Dr. Perna also criticized the methods employed by the commission in making experiments on human beings and is entirely opposed to such experiments.

DR. SAN MARTIN eloquently defended, and with strong arguments, the high scientific standard of the experiments as carried out by the commission, and also brought out the point that is was not statistics but facts that this commission presented.

DR. H.B. HORLBECK, Charleston, S.C., expressed his opinion that the problem of 200 years was about to be solved, that the old quarantine regulations should be greatly modified. He also described the existence of a pine belt within a short distance of Charleston, S.C., in which yellow fever never developed as an epidemic, although the afflicted therewith would go there during the existence of the epidemic in Charleston, would die from the disease, and yet it would not spread. Mosquitoes are not known in that region, and probably this is the true explanation of the above fact. He concluded by emphasizing the inestimable value of these experiments if they prove to be true.

DR. EMILIO MARTINEZ, Habana, laid emphasis on Dr. San Martin's views. He took up the moral question and claimed that without these no truth could be found.

DR. MANUEL GUTIERREZ, Mexico, who up until a short time had been adverse to the theory of the transmission of this disease by mosquitoes, now accepts as incontrovertible the results of the experiments of the commission. He followed with interest many of the experiments and as a member of the commission saw most of these cases, which he had no hesitation in pronouncing typical cases of yellow fever. A fact that impressed him forcibly was the absolute control of the epidemic by Dr. Reed. The cases would develop or not, as he wished. He does not think that the mosquito should be called the *Culex fasciatus*. Giles description of the *Culex tiniads* mosquito agrees more closely than with the *Culex fasciatus*. He describes the difference between them. He is inclined to consider them a genus apart because they lay different eggs.

DR. C. FINLAY, Habana, expressed his admiration for the work of the commission. He believes that this session of the congress will go down in history as of great importance and that the differences between his opinions and that held by the commission will disappear in time. He states that they were based on the fact that he investigated with three varieties of mosquitoes, while the commission has been restricted to one variety; that the board was placed on better footing for obtaining satisfactory results; that the negative result obtained by the inoculation of mosquitoes of short infection should not induce the commission or the board to make such hard and biased rules as are evidenced in its conclusions.

DR. REED, in conclusion, said he was profoundly impressed with the interest and attention given to these experiments. In regard to the moral aspect of the case, he did not think that anyone appreciated the position in which he found himself - the difficulties that beset his path. The first experiment was made on a member of the board, Dr. Carroll. The senior member expected to take his bite in turn, but was unexpectedly called north. As no animal could be given the disease, and it was useless to follow the previous indefinite experiments, it was absolutely necessary to make these experiments on human subjects, or otherwise volumes could have been written and discussed, and yet we would have been no nearer the truth than at first. No progress could have been made toward the exact knowledge of the disease unless human subject had been used. All experiment had been preformed on persons that had given their free consent.

In reference to the remarks of Dr. Holbeck, of Charleston, the disinfection of vessels should by no means be dispensed with, but only of such articles as bedding and clothing, though it is necessary to get rid of the mosquitoes, and this simplified the process of disinfection.

In regards to the remarks of Dr. Gutierrez, in reference to the name of the mosquito, Dr. Howard, of Baltimore, told him that *Culex fasciatus* is identical with *Culex tiniads* as described by Giles. Theobolt separates *Culex tiniads* from the genus *Culex* and places it in a new genus, *Stegamina*. These lay their eggs in a peculiar way, and there is also a difference in the anterior claws of the male insect from those of the *Culex*. There is also a difference in the larva of the *Culex fasciatus*. It is also very interesting to note that this is the very mosquito that Dr. Finlay used in his experiments and that this particular mosquito does not belong to the genus *Culex*; therefore malaria has a genus of its own, *Anopheles*, and yellow fever the genus *Stegamina*.

[Notes]

1. Phila. Med. Jour., Oct. 27. 1900.
2. R. La Roche: Yellow Fever, Vol. ii, p. 516, Philadelphia.

Editorial: The Etiology of Yellow Fever

The belief is growing that insects are important, even essential factors in the etiology of certain diseases. That malaria is inseparably connected with a mosquito that acts as an intermediate agent in the dissemination of the disease, has been proved definitely by suitable experiments, and the mosquito theory of malaria is in accord with the epidemiologic facts of the disease. Certain observations in the American typhoid camps of the Spanish-American War have brought the fly to the fore as a probable and dangerous carrier of typhoid fever. For some time

past great interest has been taken in the etiology of yellow fever, and since the recent studies of Reed, Carroll and Agramonte on the role of the mosquito in the disease,¹ additional data have been awaited with eagerness. Important additional evidence of the etiologic importance of mosquitoes - *Culex fasciatus*, Fabr - in yellow fever is given in the paper presented by these investigators at the recent Pan-American Medical Congress in Havana, and published in this issue of *The Journal*. A few comments on this important paper may be ventured. At first thought one might be tempted to characterize the experiments carried out on the human beings as unwarrentable, but as we are assured that everything was done with the full consent and full knowledge of the nature of the experiments on the part of the non-immunes who placed themselves at the disposal of the experimenters, there can be no adequate reason for complaint on this score. Whatever the opinion concerning this phase of the experiments, it in no way modifies the scientific value of the results. The non-immunes that allowed themselves to be bitten by mosquitoes that previously has sucked the blood of yellow fever patients, as well as the persons that slept in the "Infected Clothing and Bedding Building," seem to have submitted themselves unreservedly to the requirements of the experiments. There are examples here of unselfish devotion to the cause of humanity and of science.

The results of the experiments support the mosquito theory of yellow fever. The data are as of yet scanty for the establishment of absolute conclusions with regards to all phases of the etiology of this disease, the specific cause of which is unknown. It seems well settled, however, that mosquitoes that have fed on the blood of yellow fever patients may transmit the disease to non-immunes. No one will doubt the far-reaching importance of this demonstration! Some evidence is also brought forward to show that exclusion of the intermediate host for the parasite of yellow fever renders the disease intransmissible. The results of experiments with infected clothing and bedding must be viewed in this light. The statement that "disinfection of articles of clothing, bedding or merchandise, supposedly contaminated by contact with those sick with this disease - yellow fever - is unnecessary," seems to go a little further than the facts warrant: for it has not yet been shown that the intermediate host might not pick up, as it were, the parasite of the disease from these contaminated materials. In the future it is possible that the prevention of yellow fever may be reduced to the protection of both sick and well from the bites of *Culex fasciatus*, and the destruction of this mosquito, should it be found to be the only intermediate host capable of transmission of the disease.

[Reference]

1. Journal AMA: Nov 3, 1900, p. 1156 and p. 1170.

Historical Background: The Yellow Fever Board had expressed their appreciation for Dr. Henry R. Carter's work on yellow fever in their first paper that had been presented and published in October 1900. Walter Reed had left Cuba following presentation of their second paper on February 6, 1901 returning to Washington, DC and his position as Curator of the Army Medical Museum and professor at the Army Medical School. Along with these duties, he no doubt continued to prepare the results of the work of the Yellow Fever Board for presentation and publication. In late February he responded to a congratulatory letter with one of his own back to Dr. Carter. (This letter was contained in Dr. Carter's papers placed in the records of the United States Public Health Service and is provided courtesy of the National Library of Medicine.)

Letter: Walter Reed to Henry R. Carter, February 26, 1901

WAR DEPARTMENT,
SURGEON GENERAL'S OFFICE,
AND MEDICAL MUSEUM AND LIBRARY,
WASHINGTON.

Feb. 26, 1901.

My Dear Dr. Carter;

Please accept my sincere thanks for the sentiments expressed in your kind letter of Feb. 21st - I value highly your opinion of our work since I know of no one more competent to pass judgment on all that pertains to the subject of yellow fever. You must not forget that your own work in Mississippi did more to impress me with the importance of an intermediate host than everything else put together.

With best wishes,

Sincerely yours,

Walter Reed

[Text of letter:]

Feb. 26, 1901.

My Dear Dr. Carter:

Please accept my sincere thanks for the sentiments expressed in your kind letter of Feb. 21st. I value highly your opinion of our work. Since I know of no one more competent to pass judgment on all that pertains to the subject of yellow fever. You must not forget that your work in Mississippi did more to impress me with the importance of an intermediate host than everything else put together.

With best wishes,

Sincerely yours,

Walter Reed

Historical Background: Read by Major Walter Reed before the Sixteenth Annual Meeting of the Association of American Physicians in Washington, D.C. held between April 30 and May 2, 1901 and published in *American Medicine* 2:15-23, July 6, 1901, this article presented the remainder of the initial work that had been done at Camp Lazear in January and February 1901. The paper details the case reports of those injected subcutaneously with blood from active yellow fever patients, provides more information on the length of time an infected mosquito can transmit yellow fever, and reports in detail on signs and symptoms of the disease, as well as the time interval between exposure and onset of symptoms. This paper has been edited for space and readability. Editing consisted almost entirely of the shortening of lengthy descriptions of the yellow fever cases. An ellipsis (. . .) indicates where text has been deleted from the article. Three asterisks (***) indicate where a paragraph(s) has been deleted. Fever charts in the original article are not reproduced here.

Experimental Yellow Fever

Walter Reed, MD, Surgeon, United States Army, James Carroll, MD, and A. Agramonte, MD, Contract Surgeons, United States Army

Subsequent to the presentation of our paper to the Pan-American Congress¹ in Habana, we succeeded in producing some additional cases of yellow fever at our experimental sanitary station near Quemados, Cuba. We have thought that brief reports of these cases, to be followed by remarks on experimental yellow fever from the clinical point of view, would be of interest to the members of this association, and especially to those who reside in sections of the country where each year yellow fever is liable to appear in epidemic form.

Perhaps it might be well to recall the fact that the cases of yellow fever here to be recorded were produced like those heretofore reported by us, under strict quarantine regulations and at a special experimental sanitary station, near the town of Quemados, Cuba.

In a series of 12 experimental cases produced at this camp during the period from December 5, 1900, to February 7, 1901 — an interval of 65 days — it should be borne in mind that the order of occurrence exactly correspond with the order of inoculation, except that Case II, inoculated at 4 p.m., December 8, 1900 — having a longer period of incubation than Case III, inoculated at 10.30 a.m., December 9, 1900 — the order of their relative occurrence became reversed.² Moreover the attack always followed within the period of incubation of the disease, and concerned only those nonimmune individuals who had consented to submit themselves for experimentation. Of a total of 16 individuals who thus consented, 14 contracted yellow fever; whereas of 5 nonimmunes, who did not consent and were therefore not subject to experimentation, none acquired the disease, although otherwise placed under exactly similar surroundings. In its occurrence, therefore, at this station, yellow fever strictly obeyed the behests of the experimenters, both as to place and time of occurrence. Recovery took place in all cases.

Cases Produced by the Injection of Blood

Case I

W.J., American, nonimmune, aged 27 in quarantine since December 20, 1900 with his full consent, at 11 a.m., January 4, 1901, was injected subcutaneously with 2 c.c. of blood taken from the general circulation of a case of mild yellow fever at the beginning of the second day of the disease and having a tem-

perature of 100.8°F. The subject, who had been in strict quarantine at the station for a period of 45 days, remained in his usual health until the early morning of January 8, when he complained of slight frontal headaches. . . The subsequent history was that of a case of yellow fever of moderate severity. . .

Case II

W.O., American, nonimmune, aged 28, in quarantine since December 20, 1900. On January 8, 1901, at 9 p.m., with his full consent, he was given by subcutaneous injection 1.5 c.c. of blood taken from the median cephalic vein of Case I, just 12 hours after the beginning of the attack and when the temperature was 102.4°F., that is, just after the first febrile paroxysm began to decline. The subject remained in his usual condition during the following two days.

January 11, 1901, . . . at 12 o'clock noon, when the temperature had risen to 103.2°F. and the pulse 102, the height of the primary paroxysm had been reached. . . The character of the attack in this case was very mild.

Case III

W. F., American, nonimmune, aged 23 was, with his full consent, at 1 p.m. o'clock January 22, 1901, injected subcutaneously with 0.5 c.c. of blood taken on the second day from the general circulation of a severe case of yellow fever, which was fatal on the seventh day of the disease. The patient's temperature, when the blood was withdrawn, was 103°F. and pulse 90. The subject remained well during the following day. January 24. . . at 7 a.m. he complained of dizziness and general lassitude. . . The subsequent course was that of a case of yellow fever of moderate severity. . .

Case IV

J. H. A., American, nonimmune, aged 22, with his full consent, received subcutaneously, at 12.15 p.m., January 25, 1901, 1 cc. of blood taken from the median cephalic vein of Case III, just 27 ¼ hours after the commencement of the latter's attack of yellow fever (T. 100.6°F.). The subject remained in his usual condition during January 26 and 27, except that on the afternoon of the last-mentioned date he complained of occipital

headache. . . Ocular jaundice appeared on the third day. The skin of the face and of the anterior part of the neck and thorax was tinted on the fourth day. This rapidly became intensified and general. . . Marked fluctuations of temperature continued until the eleventh day of illness. Recovery was slow and much delayed by the development of a carbuncle in the left sacral region. . .

The production of yellow fever by the injection of blood taken from the general circulation is of much interest as showing, first, that the parasite is present in the blood, at least during the early stages of the disease, and secondly, that its passage through an intermediate host, although this would seem to be nature's method, is not essential in the life cycle of this parasite. Thus yellow fever is analogous to the malarial fevers, in that it may be produced either by the bite of a certain species of mosquito, or by the injection of blood taken directly from the general circulation.

Another point to which we have elsewhere referred, but which is considered of sufficient importance to bear repetition here, is that in each of the foregoing cases of experimental yellow fever produced by the injection of blood, careful cultures made from the same blood drawn from the vein immediately after injection or, as in one instance, made from the same syringeful of blood that conveyed the disease, failed to show the presence of Sanarelli's bacillus. In one case colonies of *Staphylococcus pyogenes citreus* were obtained, while in the remaining three cases no growth whatever occurred. The exclusion of *Bacillus icticoides* from further consideration as the specific agent of yellow fever would, therefore, seem to have been conclusively determined by these experiments.

Cases Produced by the Bite of the Mosquito, *Culex fasciatus*

Case V

L.F., American, nonimmune, aged 28 — in quarantine since December 20, 1900 — was, with his full consent, at 3.30 p.m., January 19, 1901, bitten by three mosquitoes that had been contaminated 39 days previously, by feeding on the blood of a well-marked case of yellow fever, on the third day of the disease. The subject remained in his usual condition of health until the afternoon of January 23. . . he took to his bed, complaining of frontal headache and general lassitude. . . The case was one of moderate severity. . .

Case VI

C.W., American, nonimmune, aged 27, with his full consent, was at 9.30 a.m., January 31, bitten by 2 of the 3 mosquitoes that had been applied to the foregoing Case V. The interval that had elapsed since their contamination was, therefore, 51 days. The subject remained well until 12 o'clock noon, February 3, when he complained of heaviness in his legs and some supraorbital pain. . . The case was mild in character. . .

Case VII

J.H., American, nonimmune, aged 26, with his full consent, was bitten at 11 a.m., February 6, 1901, by the same 2 mosquitoes that had 6 days previously bitten Case VI. Fifty-seven days had therefore elapsed since the insects had been contaminated

by biting a case of yellow fever. He remained well until 12 o'clock noon, February 9, when he experienced slight chilly sensations. . . The subsequent course was that of a case of severe yellow fever. . .

Case VIII

C.S., American, nonimmune, aged 28, with his full consent, was bitten at 2 p.m., February 7, 1901, by 3 mosquitoes that had been contaminated 16 days previously by biting a fatal case of yellow fever on the second day of the disease. The subject remained well until the early afternoon of the third day. . . he had severe headache and backache, with general pains over the body. . . photophobia well marked, and face decidedly congested. . . Ocular jaundice was slight. . . Convalescence was rapid. . .

The foregoing cases of experimental yellow fever (Case V, VI, and VII) are, we think, of especial importance as showing the length of time during which the mosquito may remain capable of conveying the infection. In previous papers we have reported 6 cases of yellow fever produced by the bites of mosquitos at intervals varying from 12 to 24 days after the contamination of the insects. In the cases here reported the periods intervening between the contamination of the insect and the production of the disease were much longer, viz, 39, 51, and 57 days respectively. As one of these insects lived until the sixty-ninth and another until the seventy-first day after contamination, we have for the first time an explanation of the fact, several times noted in the literature, that the contagion of yellow fever may cling for several months to a building that has been vacated by its occupants, or to the infected area of a town, even though this latter has been entirely depopulated. These particular insects also were contaminated at a later stage of the disease than in any of our other cases, i.e., on the third day and during the secondary rise of fever, following a complete intermission in the temperature. We have, therefore, been able to demonstrate that the parasite is present in the general circulation both after and before the stage of remission. How much later in the disease the parasite may still be found — a matter of much interest and importance — the observations thus far made do not determine. Although the 3 mosquitoes applied on the third day, as above state, acquired the parasites and were able to affect 3 individuals with yellow fever, a single mosquito applied to the same case of yellow fever on the fourth day of the disease failed to obtain the parasite, as shown by the negative result following its bite 40 days after contamination. That not all mosquitoes become infected, however, with the parasite by biting yellow fever patients is shown by several observations made by us. We submit only one.

Case IX

J.W., American, nonimmune, was, with his full consent, on January 25, 1901, bitten by 12 mosquitoes (*C. fasciatus*) that had fed on a case of mild yellow fever — in a man named Martinez — on January 3, 1901, within 8 hours of the commencement of the attack. Although these mosquitoes had been kept at a summer temperature for 22 days, the result of the experiment was entirely negative. That the parasites were present in Martinez's blood at the end of 24 hours was fully shown by the effect produced by injecting 2 c.c. of his blood drawn at this time beneath the skin of Case I of this report.

Observations such as the foregoing would indicate that the

mosquito at certain periods of the disease may fail to obtain the parasite, owing to its absence at that particular time from the capillary circulation. Concerning the matter of the propagation of yellow fever by other species of culex than *C. fasciatus*, we have only 1 negative observation to record of an individual bitten by 5 *C. pungens* that had been contaminated by biting a case of yellow fever 19 days previously. To a single negative experiment such as this not importance can be given, so that this question must be left for future observations to determine.

Touching the subject of the possible transmission of the parasite to the daughter insect by means of infection of the ovum, we have also but a single observation to record. In this case the bites of 14 mosquitoes, hatched from the ova of a mosquito (*C. fasciatus*) that had already shown itself capable of conveying the disease, were followed by an entirely negative result.

Including the cases heretofore reported by us, we have thus far succeeded in conveying yellow fever to 12 individuals by means of the bites of contaminated mosquitoes, and to 4 other persons by subcutaneous injection of blood taken from cases of this disease — a total of 16 cases. While ordinarily so small a number of cases would not be sufficient to enable one to arrive at definite conclusions concerning the general character and course of an acute infectious disease, the conditions under which the majority of these cases were observed were such as to give us valuable data concerning two matters of very great practical importance in connection with this disease, viz, the period of its incubation and the difference in degree in the character of its attacks. Further, as these cases were kept under constant observation, even from the time of inoculation, we are not only able to report upon the earliest premonitory symptoms, but also to give the primary temperature curve; and, in addition, to note the time of appearance of albumin in the urine, all of which are of interest in the clinical history of yellow fever.

Period of Incubation

The accurate determination of the period of incubation of any one of the acute infectious diseases is always a matter of scientific interest. If the disease is one which, like yellow fever, is of exotic origin and who importation is liable to give rise to a

widespread epidemic, then the determination of its incubative stages becomes of the highest practical importance. This importance, as a question of public hygiene, is increased, if as recent observations would seem to indicate, the importation of this disease is brought about only by the sick individual and not by his baggage or clothing. While the older authors were willing to prolong the period of incubation of yellow fever to 2 or 3 weeks or even longer, the tendency of physicians at the present time is to shorten this stage to about 5 days. Reference to a few of the later text-books on the Practice of Medicine will sufficiently indicate this. Davidson, in Allbutt's System,³ puts down the period of incubation as "ranging between 24 hours and 4 or 5 days." Stevens⁴ says that it may vary from "a few hours to a week." Osler⁵ says that "the period of incubation is usually 3 or 4 days, but it may be less than 24 hours or prolonged to 7 days." According to Tyson,⁶ "yellow fever has a period of incubation of from 24 hours to 5 days, very rarely exceeding the latter." Sternberg⁷ says that this period "does not usually exceed 4 or 5 days and may be less than 24 hours." Carter,⁸ in a recent valuable paper, gives the results of his studies on the period of incubation of yellow fever, based on observations extending over a considerable number of years. Under Class III of his observations, which are the most valuable, he includes "those persons who, living in a clean environment, go into an infected one, stay only a short time, and then return to a clean environment where they remain until the fever develops." Of 12 cases thus accurately observed by himself the incubative stage was as follows: 2 cases, 3 days; 6 cases, 3+ days; 2 cases, 4 days; 1 case, 4½ days; and 1 case, 5¼ days.

The following table gives the result of our observations in 16 cases of experimental yellow fever (Table I).

The average period of incubation of the 16 cases embraced in Table I will be found to be 87¼ hours, or 3 days 15¼ hours. If we separate the 12 mosquito infections from the 4 cases produced by the injection of blood, we have for the former a period of incubation of 94 hours or 3 days and 22 hours, and for the latter an incubative stage of 67½ hours, or 2 days 19½ hours. The average period of blood was shorter by 26½ hours than those occasioned by the mosquito's bite. By the former method,

TABLE I
PERIOD OF INCUBATION OF EXPERIMENTAL YELLOW FEVER

No. of Cases	Date of Inoculation	Method of Inoculation	Date of Commencement of Attack	Incubation	
				Dys.	Hrs.
1	Aug. 27, 1900, 2 p.m.	Mosquito	Aug. 31, 1900, 9 a.m.	3	7
2	Aug. 31, 1900, 11 a.m.	"	Sept. 6, 1900, 1 p.m.	6	2
3	Dec. 5, 1900, 2 p.m.	"	Dec. 8, 1900, 11.30 p.m.	3	9½
4	Dec. 8, 1900, 4 p.m.	"	Dec. 14, 1900, 9 a.m.	5	17
5	Dec. 9, 1900, 10.30	"	Dec. 12, 1900, 9.30 p.m.	3	11½
6	Dec. 11, 1900, 4.30	"	Dec. 15, 1900, 12 noon	3	19½
7	Dec. 21, 1900, 12 noon	"	Dec. 25, 1900, 11 a.m.	3	23
8	Dec. 30, 1900, 11 a.m.	"	Jan. 3, 1901, 10.30 a.m.	3	22½
9	Jan. 4, 1901, 11 a.m.	Blood injection	Jan. 8, 1901, 9 a.m.	3	22
10	Jan. 8, 1901, 9 p.m.	"	Jan. 11, 1901, 9 a.m.	2	12
11	Jan. 19, 1901, 3.30	Mosquito	Jan. 23, 1901, 3 p.m.	3	23½
12	Jan. 22, 1901, 1 p.m.	Blood injection	Jan. 24, 1901, 9 a.m.	1	19
13	Jan. 25, 1901, 12.15	"	Jan. 28, 1901, 1.15 p.m.	3	1
14	Jan. 31, 1901, 9.30 a.m.	Mosquito	Feb. 3, 1901, 12 noon	3	2½
15	Feb. 6, 1901, 11 a.m.	"	Feb. 9, 1901, 5 p.m.	3	6
16	Feb. 7, 1901, 2 p.m.	"	Feb. 10, 1901, 12 noon	2	22

this stage varied from 43 hours to 94 hours, while in the mosquito infections the shortest incubative period was 70 and the longest 146 hours. If we accept those cases produced by the mosquito's bite as the usual method of propagation of this disease, it will be observed that of the 12 cases 1 occurred on the third day, 9 on the fourth day, 1 on the sixth day, and 1 at the beginning of the seventh day after incubation.

While our results, therefore, confirm the statement of later writers that the period of incubation of yellow fever does not usually exceed 4 or 5 days, they also seem to indicate very plainly that this stage may be prolonged more frequently, perhaps, than had been supposed.

In 16.6 per cent of our cases the period of incubation exceeded the usual quarantine period of 5 days. If we add Carter's cases to those observed by us, we find that of 24 cases the period of incubation exceeded 5 days in 3, or 12.5 per cent. We will not further dwell on this subject than to remark that cases No. 2 and No. 4 of our series could have passed quarantine on the morning of the sixth day after inoculation, with a clinical thermometer under the tongue, without exciting any suspicion by reason of the presence of fever.

Character of the Attack

We desire to call attention particularly to the difference in the degree of severity of the attack as shown by our experimental cases. Like all of the other acute infectious diseases, we have reason to expect that yellow fever will affect different individuals according to their individual susceptibilities, and hence that we will encounter mild as well as severe cases. The results which we have obtained confirm this expectation. Based upon the character of the attacks, the 12 cases due to mosquito inoculation may be divided as follows: [Severe 2, moderately severe 6, mild 3, and very mild 1.] The 4 cases produced by the injection of blood gave the following result: [Severe 1, moderately severe 2, and mild 1.]

Thus the cases which were mild or very mild in character constituted 33 per cent of those infected by the mosquito's bite and 25 of those produced by blood injection. It is to the diagnosis of the former cases that we desire to direct special attention. To one familiar with yellow fever, or even to one unfamiliar with its clinical features, the diagnosis of our severe and moderately severe cases should have presented no difficulty. The sharp headache and backache, the characteristic facies, the ocular jaundice, together with the presence of albumin in the urine, except in 1 case to be hereafter referred to, with the negative result of a blood examination, would have been a sufficient complex of symptoms to have rendered the diagnosis tolerably certain. Even in our 3 "mild" cases, were the physician on his guard and acquainted with the temperature curve and pulse from the very onset of the attack and, besides, careful in the testing of each specimen of urine passed, a diagnosis of yellow fever could have been made with reasonable probability. We believe, however, that, in the ordinary course of events, where there was no reason to suspect the presence of yellow fever the average practitioner would have probably failed to appreciate the true nature of these attacks. Such was the admission which we ourselves were compelled to make, although in constant attendance and thoroughly acquainted with these cases from their very beginning. The short duration of the primary fever in one instance; the rapid amelioration of the earlier symptoms in

all; the absence of albumen during the first 3 days, or its presence, as a mere trace, in certain specimens, followed by its absence in succeeding specimens; the slight icteroid line of the conjunctiva — to be obtained only in a certain light and then doubtfully — all served to render a positive diagnosis exceedingly difficult. Several physicians, who saw these milder cases at our request, readily acknowledged the improbability of a correct diagnosis being made in the absence of the complete data which we were able to furnish concerning them. In the one case which we have classed as "very mild" yellow fever we believe that the matter of a correct diagnosis would have been in the highest degree improbable. . . . That cases of mild yellow fever may and do serve as foci for the development of other cases our own observations demonstrate, since we have been able to propagate the disease from one such mild case by means of the bites of contaminated mosquitoes, and from another case of like character by the subcutaneous injection of 2 c.c. of blood.

The Onset and Premonitory Symptoms

Of the 12 cases produced by mosquito inoculation, the onset was sudden in 2 and gradual in 10. In both of the former the attack occurred during the night, the patient, also, in both instances, being awakened by the occurrence of a decided chill. In 1 of the 2 cases of sudden onset, the subject complained of slight supraorbital headache during the afternoon preceding the attack. Of 4 cases produced by the injection of blood, the onset was sudden in 1 — the only case marked by a chill — and gradual in 3. The attack in all of these blood cases began during the daytime. As writers generally state that in yellow fever the chances of infection are greater during the night, we have thought that, perhaps, the time of inoculation of our experimental cases (which was during the day except in 1 instance), might have had some influence upon their occurrence, as a rule, during the daytime. If the hour of inoculation in all of our cases should have taken place at about sunset, then, with the same period of incubation, 7, or 43 per cent would have experienced their attacks at night.

Of the 13 cases in which the onset was gradual — by mosquito inoculation, 10; by blood injection, 3 — frontal headache, the pain being referred to the supraorbital region and extending into the temporal region, was the most frequent premonitory symptom. It was present in 10 and absent in 3 cases. This symptom preceded the attack in these cases at intervals varying from 2 to 48 hours. In 2 cases no premonitory headache was complained of, while in 1 case occipital headache preceded the onset by 24 hours, and continued to be of this character throughout the attack. Dizziness was complained of by 3 of the gradually developing mosquito cases, and a sense of weight in the lower extremities by the 2 others belonging to this group. All of the cases of gradual onset (13 in number) complained of lassitude and want of appetite, on which account all took to their beds prior to the onset of fever. Ten of these individuals complained of slight sensations of chilliness — generally confined to the lower extremities — at the beginning of the attack, while in 3 this symptom was entirely absent. In our experimental cases, therefore, frontal headache and muscular debility were the most frequent and prominent premonitory symptoms. After the attack had developed, the symptoms correspond to those described at

TABLE II

Case	Albumin During Period of Incubation	Time of Appearance of Albumin During the Attack (Hours)	Time of Disappearance of Albumin Dating from Appearance	Maximum Quantity
Mosquito inoculation:				
1	None	42	Tenth day	Eight-tenths by volume.
2	None	25	Eleventh day	Three-tenths by volume.
3	None	82 ½	Fifteenth day	Two-tenths by volume.
4	None	48	Fifth day	Distinct trace.
5	None	64 ½	Fourth day	Light trace.
6	None	43 ½	Third day	Distinct trace
7	None	37 ½	Eighth day	Do.
8	None	43	Ninth day	One-fortieth by volume
9	None	42	Twelfth day	One-twentieth by volume
10	None	75	Eighth day	Distinct trace.
11	None	106	Fifteenth day	One-fortieth by volume
12	None	None	(¹)	One-twentieth by volume
Blood inoculation:				
13	None	61	Thirteenth day	Distinct trace.
14	None	17	Twelfth day	Do.
15	None	57	Ninth day	Do.
16	None	18 ½	Fifteenth day	One-tenth by volume

¹Albumin did not appear till 36 hours after fever had subsided and persisted for five days.

length by various writers and with which are familiar, except that black vomit did not occur in any of our cases.

The Fever

As we have had prepared charts of our several cases of experimental yellow fever, from which all the data concerning temperature and pulse can be obtained, it will not be necessary for us to make extended remarks under this heading. Medication being practically nil in our cases, both temperature-curve and pulse can be accepted as faithfully representing what normally takes place in an attack of this disease. When ice water enemas or cold sponge baths were used by the attending physician, this is noted on the chart. It should also be remembered that our patients were put to bed at the very first manifestation of the disease, and carefully transported to the yellow-fever wards on the very same beds which they had occupied in camp. This probably had some effect upon the subsequent course of the fever. The record of temperature being taken every 3 hours from the time of inoculation enables us to give the complete curves of both the primary and secondary febrile paroxysm. Our charts therefore differ considerably from those given by the various writers on yellow fever in that they round out, as it were, the primary stage more fully. An examination of these charts will show that although the primary rise of temperature is tolerably abrupt and reaches its height within a comparatively short time, it does not reach its maximum so quickly as the description of writers would seem to indicate. The trihourly record in 10 of our mosquito inoculations shows that this period of primary rise varies from 12 to 24 hours. . . The average period of the 10 cases was therefore a fraction over 16 hours.

In striking contrast to these was the short period of the primary rise of temperature in the 4 cases produced by blood injection. In these it varied from 2¼ to 9 hours, the remaining 2 cases giving 6 and 7 hours respectively, the average for the 4 cases being only 6 hours. In all of the 12 cases due to mosquito

inoculation, the primary rise of temperature was followed by a distinct remission or intermission, which was generally reached within 48 hours. The same remission was present in 3 of the 4 cases produced by blood injection. We are able to give the duration of the primary paroxysm accurately in the 10 cases produced at Camp Lazear by the bites of mosquitos, viz.: There was one case each at 33, 33½, 36, 39, 41, 52, and 60 hours and three cases at 45 hours.

The average duration of these 10 cases was 43 hours. In the 3 cases caused by the injection of blood the length of the primary paroxysm was 24 hours in 2 cases and 36 hours in 1 case — the average being 28 hours. We may therefore say that not only the average period of incubation, but also the primary rise of temperature, as well as the length of the first febrile stage were all shorter in the cases produced by blood injection than in those due to mosquito's bite. Of the 12 cases due to the latter mode of inoculation the first febrile stage was followed by an intermission in 2, and a remission in 10 cases. Of those produced by the injection of blood, 3 showed a distinct remission and 1 no intervening fall of temperature. The duration of this intermission varied from 3 to 27 hours. This was followed by a second febrile stage or paroxysm in 11 of the 12 mosquito inoculations, and in 3 of the 4 cases due to the injection of blood. The duration of this second febrile paroxysm was from 2 to 5 days.

Experimental yellow fever then, as we saw it at Camp Lazear, consisted of a primary and secondary febrile paroxysm, with an intervening remission or intermission — more frequently the former. The secondary was much longer than the primary febrile stage.

In 1 of our mosquito inoculations a relapse occurred on the ninth day of the disease, and was characterized also by 2 febrile stages with an intervening remission. There were present headache and backache, with injection of the eyes and face, together with hemorrhage from the gums, as had been observed in the primary attack.

The want of correlation between temperature and pulse (Faget's law), upon which clinicians rely as an important diagnostic sign, was seen as a rule in our experimental cases, i.e., after the passage of the first febrile stage. In 1 case produced by the injection of blood, Faget's law was not complied with.

The Urine

We have confirmed our examination of the urine largely to testing for the presence for albumin and to the ordinary microscopic examination of this fluid. Heat and nitric acid was the method used in all cases for the detection of albumin, the specimen having first been carefully filtered.

Under this heading we desire to speak only concerning the presence of albumin. All writers dwell on the importance of a careful examination of the urine in suspicious cases of fever, since the presence of albumin in the urine is such a constant sign in yellow fever. Guiteras, who has had a large experience with this disease, says: "The albumin appears in the urine usually on the third or fourth day of the disease. It may be very transient. In many mild cases the albumin is present only in the urine passed in the evening of the third or fourth day. In many cases it is only a trace." We may say that the results obtained from examination of the urine of experimental yellow fever accords for the most part with the statements above quoted.

In our earlier cases we did not examine for albumin until the onset of the attack. In our last 8 cases (those embraced in this report) we examined daily specimens from the time of inoculation until the attack began, and thereafter we endeavored to examine every specimen passed by the patient. Table II gives the results obtained.

It will be observed that the quantity of albumin present in this series of cases was very moderate, except in Cases I and II of Table II. These cases were the only 2 of the 16 that were not placed in bed from the very beginning of the attack. In the remaining 14, all of whom were kept at absolute rest during the

whole period of the fever, the amount of albumin was small in 6 and insignificant in 8. We are inclined to believe, therefore, that both the course of the fever, as well as the quantity of albumin, were favorably affected by the early enforced rest of our patients.

In conclusion we desire to invite attention to 2 matters which we consider of considerable importance in connection with the possible importation and propagation of yellow fever. First, we believe that the facts herewith presented indicate that the period of incubation of yellow fever occasionally exceeds the quarantine period of 5 days, and that although exceptional this must not be left out of consideration. Secondly, that our observations emphasize anew the importance of the recognition by the profession of mild and very mild cases of yellow fever. Guiteras⁹ says: "I cannot insist too much upon the importance of the diagnosis of the first case of yellow fever in a locality." He adds: "Undoubtedly the cause of the epidemic of yellow fever is to be found in the introduction into a community of cases that are not suspected to be yellow fever." In the light of our investigations, we feel constrained to remark that the failure to detect cases of mild yellow fever has been, we believe, the most important factor in the development of the theory of the propagation of this disease by fomites.

[Notes]

1. The Etiology of Yellow Fever. An Additional Note: Read at the Pan-American Congress. Habana, February 4-7, 1901.
2. These cases were reported in our Additional Note.
3. A System of Medicine, London, 1897, Vol. II. p. 394.
4. Practice of Medicine, Philadelphia, 1898, p. 286.
5. The Practice of Medicine, New York, 1899, p. 185.
6. Practice of Medicine, Philadelphia, 1900, p. 85.
7. Buck's Reference Handbook of the Medical Sciences, 1889, Vol. III, p. 58.
8. The Period of Incubation of Yellow Fever, New York Medical Record, March 9, 1901.
9. Report of United States Marine-Hospital Service, Vol. XX-VII, 1897-1898, p. 300.

Historical Background: All of those involved in the work of the Yellow Fever Board were very interested in continuing the effort to isolate the agent of yellow fever. Dr. William H. Welch, the distinguished professor from Johns Hopkins who had instructed Reed and Carroll during their earlier studies at Hopkins, had followed the work of the Board closely. He brought to their attention the research of Löeffler and Frosch who had demonstrated that the agent of hoof and mouth disease in cattle was ultramicroscopic and passed through the smallest known filter. Reed and Carroll were eager to continue their research and sought permission to return to Cuba to conduct studies to determine if the yellow fever organism was possibly similar.

After Reed and Carroll had left Cuba in February 1901, Dr. Juan Guit  ras, a Cuban yellow fever expert, began some experiments at Las Animas Hospital in Havana attempting to vaccinate against yellow fever by producing mild cases with the bites of "loaded" mosquitoes. In August 1901 he produced several cases with tragically, three deaths, including the American nurse Clara Maass. These deaths ultimately lead to an order to suspend experimentation on American soldiers.

Only James Carroll was granted permission to return to Cuba; he arrived in August 1901 just the week before Clara Maass died. Despite these extremely unfortunate deaths, he was determined to press on. Because of the high level of anxiety over these recent events, it was not practical for Carroll to use yellow fever cases from Havana, so he borrowed some loaded mosquitoes from Juan Guit  ras and produced his own new cases. He knew from his earlier experiments that yellow fever could be transmitted by injection of whole blood and he wanted to determine if the agent of yellow fever was filterable.

After just a little over 2 months back in Cuba, this cryptic cable sums up his findings and plans (Fig. 1). Two hours after he sent this cable, Carroll injected what was to be the third and last case produced by serum filtrate. John R. Bullard, an American living in Cuba, had been treated by Carroll for malaria and subsequently had volunteered for the yellow-fever experiments. His was the last case of yellow fever produced by the efforts of the U.S. Army Yellow Fever Board; he recovered. Bullard appears as Case X and is referred to as J.R.B. and J.M.B (an apparent typing error) in Reed and Carroll's, *The Etiology of Yellow Fever — A Supplemental Note*, which is reprinted in *Military Medicine* 166: Suppl 1, 2001.

Cable: James Carroll to The Surgeon General, October 22, 1901*

1516. CABLE MESSAGE.
THE WESTERN UNION TELEGRAPH COMPANY.
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 All CABLE MESSAGES received for transmission must be written on the Message Blanks provided by this Company for that purpose, under and subject to the conditions printed thereon, and on the back hereof, which conditions have been agreed to by the sender of the following message.
 THOS. T. ECKERT, President and General Manager.

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RECEIVED WAR DEPARTMENT.

Oct, 22nd, 1901. 189

8 CO. G. KN. Government.

Havana 27.

Surgwar,

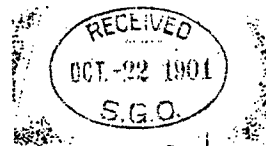
Washington.

Filtrate positive in two apparatus perfect, temperature results ideal three cases five in all outlook very favorable, close up return ten days.

Carroll,

Contract Surgeon.

12:52 P.M.



*Original document resides in Record Group 112, National Archives and Records Administration.

Historical Background: This is the last article published on the original research work of the U.S. Army Yellow Fever Board. It was read before the third annual meeting of the Society of American Bacteriologists, Chicago, IL, December 31–January 1, 1902 and published in *American Medicine*, p 301–305, February 22, 1902. The cases described in this paper were solely due to the work of Dr. James Carroll after he returned to Cuba in August 1901. Carroll continued his work at the Las Animas Hospital in Havana, despite Reed's concern about the further risking of lives after the deaths of three volunteers. One of the deaths was the American nurse Clara Maass, who had participated in the experimental work of Cuban yellow fever expert, Dr. Juan Guit  ras. The paper reports another very interesting and landmark discovery — the first transmission of a human disease by a filterable agent — demonstrating that the etiological agent of yellow fever was an organism smaller than a bacterium. This paper has also been edited for space and readability. Editing consisted almost entirely of shortening lengthy descriptions of the yellow fever cases. An ellipsis (. . .) indicates where text has been deleted from the article. Six fever charts in the original article are not reproduced here.

The Etiology of Yellow Fever: A Supplemental Note

Walter Reed, MD, Surgeon, United States Army; and James Carroll, MD, Contract Surgeon, United States Army, Washington, DC

In former contributions to this subject, we have shown by observations made on human beings that yellow fever may be produced in the nonimmune individual either by bite of the mosquito¹ (genus *Stegomyia*) that has previously been permitted to fill itself with the blood of a patient suffering with yellow fever, during the first three days of the attack, or by the subcutaneous injection of a small quantity of blood² (0.5 to 2 c.c.) drawn from the general circulation of such a patient during the active stage of this disease. For further particulars regarding these observations the reader is referred to the original papers.

Although these experiments have demonstrated that the specific agent of yellow fever is present in the blood, we may say that the prolonged microscopic search which has been made by other investigators, as well as by ourselves, both with fresh and stained preparations of blood, taken at various stages of this disease and during early convalescence, has proved thus far entirely negative. We may add that the efforts which we have made with reasonable hope of reward, both in the bodies of infected mosquitoes, dissected in the fresh state, as well as by serial sections of the hardened insect, have likewise given no results which we consider worthy of record at the present time. Leaving out of consideration, therefore, for the time being, the further microscopic search for the specific agent in the blood of the sick and in the bodies of infected mosquitoes, we desire to call attention to some additional observations bearing on the etiology of the disease, which one of us (Carroll) has recently made at Las Animas Hospital, Habana, Cuba, and at Columbia Barracks, near Quemados, Cuba.

We here desire to express our sincere thanks to Dr. William H. Welch, of the Johns Hopkins University, who, during the past summer, kindly called our attention to the important observations which have been carried out in late years by Loeffler and Frosch relative to the etiology and prevention of foot-and-mouth disease in cattle. In the course of their investigations concerning a reliable method of immunization in this disease, the authors had occasion to dilute and afterwards to pass several times through a porcelain filter, lymph which had been collected from the blebs present in the mouth and on the feet of cattle sick with foot-and-mouth disease.³

These observers, having already ascertained that immunity could be conferred upon cattle by the subcutaneous or intrave-

nous injection of one-fortieth to one-fiftieth c.c. of pure lymph previously mixed with 1 c.c. of the defibrinated blood of an animal that had recently recovered from the disease, desired to find out whether the injection into calves of given quantities of this filtered and bacteria-free lymph would not, also, enable them to confer immunity of, perhaps, a higher degree upon cattle.

The results were quite surprising, since it was shown that calves which had received one-tenth to one-fortieth c.c. of the diluted and filtered lymph developed foot-and-mouth disease just as promptly as calves that had been injected with corresponding quantities of the unfiltered lymph.

According to Loeffler and Frosch, there were two possible explanations of this remarkable result; either that the filtered lymph held in solution an extraordinary active toxin, or that the specific agent of the disease was so minute as to pass through the pores of a filter which prevents the passage of the smallest known bacteria.

The authors accept the latter explanation, since they were able, in later experiments,⁴ by means of the filtered lymph, to convey the disease through a series of six animals, the last of which sickened just as promptly after the injection of the filtered lymph as the first of the series.

Having, therefore, conclusively determined that the microorganism of foot-and-mouth disease of cattle is so extremely minute as to pass readily through a porcelain filter, it was natural that Loeffler and Frosch should have put forward the suggestion that, perhaps the specific agent of some of the acute infectious diseases of man and animals, such as smallpox, scarlet fever, measles, rinderpest, etc., might also belong to this group of ultramicroscopic organisms.

It was for the purpose of ascertaining whether observations conducted along the same lines as those above mentioned might throw additional light upon the etiology of yellow fever that the following experiments were undertaken.

Of course it will be thoroughly appreciated that in experimentation on human beings, aside from the grave sense of responsibility, at times well-nigh insupportable, which the conscientious observer must always feel, even with the full consent of the subjects to be experimented upon, there must be added another

factor, viz, the difficulty of finding willing and suitable nonimmune individuals for experimentation just at the proper and urgent moment. It so happened that on the day of Dr. Carroll's arrival at Habana, August 11, 1901, the first patient of the series of seven cases of yellow fever which Dr. Guit  ras⁵ had produced by bites of infected mosquitoes, was taken sick. The fatal termination of three of these cases produced a somewhat panicky feeling toward experimental yellow fever among the nonimmunes at Habana, which feeling was intensified by the sensational and distorted statements in one of the local Spanish papers. It was, therefore, extremely difficult in fact, practically impossible to obtain for inoculation purposes persons who could with reasonable certainty be regarded as nonimmunes.

Further, as it was not practicable to withdraw blood from any case of yellow fever under treatment in the city of Habana, it became necessary to produce cases by means of the bites of infected mosquitoes — *Stegomyia fasciata* — accepting such subjects as were willing to submit to this mode of inoculation. In all six individuals, supposedly nonimmunes, were bitten by mosquitoes, of whom four gave a negative and two a positive result.

The Following Are the Negative Cases

August 14, 1901

S.V., Spaniard, resident of Habana for a few months, was bitten by two insects that had been applied to a yellow fever patient 34 days previously. Result negative, although the bites of two mosquitoes from this same lot had already infected an individual, who later died of yellow fever.

September 5, 1901

J.T., American, was bitten by nine insects that had been applied to a mild case of yellow fever on the second day of the attack, 23 days before. He was again bitten 30 days later by four mosquitoes that had been applied to a moderately severe case of experimental yellow fever 11 days before. The result of both inoculations were negative. This man had resided one year in Central America, and we were afterwards informed that he had confessed to a previous attack of the disease.

September 11, 1901

A.P., Spaniard, was bitten by three insects which 53 days previously had bitten patient with a typical case, on the third day of the attack. These were among a lot of mosquitoes that had already infected three individuals, two of whom died of yellow fever. The result was negative. Five weeks later he received a subcutaneous injection of about one-fourth c.c. of blood drawn from a patient with a mild case of yellow fever, on the second day of illness. Result negative. The previous history of this man was not satisfactory, as he had recently returned from a residence in Mexico.

September 9, 1901

A.V., Spaniard, was bitten by three mosquitoes that had been applied to a mild case of yellow fever on the second day of the attack, 27 days before. Three weeks later he was again bitten by one mosquito 49 days after it had been applied to a fatal case of yellow fever, on the third day of the attack. The result of both inoculations was negative.

We Give Brief Sketches of the Two Positive Cases

Case I

P.R.C., a Spaniard, had served in the Spanish army in the Philippines. He arrived in Habana from Spain about August 30.

On September 16, 1901, he was bitten at 4 p.m. by 4 mosquitoes that had previously fed upon cases of yellow fever as follows: One had bitten a patient having a fatal case, on the third day of the disease, 53 days before, and 3 had bitten a patient having a fatal case, on the second day of illness, 34 days previously. His attack began at 4.30 p.m., September 19, after an incubation period of 72½ hours. At the onset he experienced a slight chill with rigors and loss of appetite. Later in the evening he complained of slight frontal headache and pains in the lumbar region. On the following day the headache and backache were more severe. At 10 a.m. he vomited about 6 drams of slightly greenish fluid containing mucus. On the second day of the attack the gums were swollen, pale, and spongy, and there was soreness upon deep pressure over the epigastric and hypogastric regions; the face was flushed and the eyeballs were slightly yellow. September 24, fifth day, he was well jaundiced, epigastric and abdominal soreness were pronounced, and there was nausea with eructations. At this time an unfavorable prognosis was given by two physicians of large experience in yellow fever. Happily, with the decline of temperature on the sixth day, the symptoms were much ameliorated and the patient made an uninterrupted recover. . .

Early on the second day blood was drawn from the median-basilic vein with all precaution and 10 drops were immediately added to each of four flasks containing 200 c.c. of sterile nutritive bouillon. The flasks were kept under observation in the incubator and at room temperature for 14 days without the development of any growth. At the end of that time each flask was agitated and an agar slant was freely inoculated with fibrin and fluid from its contents. These cultures remained sterile 16 days later after being kept four days in the incubator and 12 at room temperature.

On the second day, blood was drawn for the purpose of obtaining serum for filtration, but owing to an accident to the vacuum pump the experiment had to be abandoned.

Specimens of the fresh blood were examined for malarial parasites, with negative results, on the second and fourth days of the attack.

Case II

J.M.A., Spaniard, recently landed at Havana, was bitten at 4 p.m. October 9, by 8 mosquitoes that had been applied to a severe case of yellow fever (Case I) on the second day of the disease, 18 days previously. The attack which followed was mild. . . The case pursued a mild course, the temperature falling to normal at 9 p.m. of the fourth day.

On October 15, 11.30 a.m., at the beginning of the third day of illness, the temperature was 101°F.; 65 c.c. of blood were drawn, with antiseptic precautions, from a vein at the bend of the elbow. This was placed in a sterile test tube and set aside in the refrigerator. At 6 a.m., 5½ hours later, 19 c.c. of a slightly bloodstained serum were pipetted off into another sterile tube. After the addition of an equal quantity of sterilized distilled water the diluted serum was slowly filtered through a new

Berkefeld laboratory filter that had been subjected to previous sterilization in an Arnold's sterilizer. In this way 35 c.c. of a slightly bloodstained filtrate were obtained, a part of which was subsequently used for the inoculation of VII, VII, and IX of this report.

The original level of the blood having been marked upon the tube into which it was drawn, a sufficient quantity of sterilized distilled water was then added to replace the 19 c.c. of serum that had been pipetted off and to make up the original volume of blood. The whole, consisting of clot, remaining serum, and distilled water, was poured into a sterile vessel and whipped up with a sterilized egg beater. The mixture, which approximately represented the partially defibrinated blood, was then divided into two parts, one of which was reserved for the inoculation of a control subject (Case III), while the other part was placed in a double water bath previously heated, and exposed to a temperature of 55°C. for 10 minutes. It was then removed and immediately cooled in ice water. This cooled material was subsequently used for the injection of Cases IV, V, and VI.

It will thus be seen that we have at our disposal, for purposes of inoculation, three kinds of materials, derived from the blood in Case II, viz: (a) The unheated and partially defibrinated blood; (b) the partially defibrinated blood which had been heated to a temperature of 55°C. for 10 minutes, and (c) the diluted blood serum which had been filtered through a Berkefeld filter. Each of these materials was used for the inoculation of one or more nonimmune individuals with the results that follow herewith.

(a) The Unheated and Partially Defibrinated Blood

Case III

M.G.M., Spaniard, arrived at Habana October 4, 1901. At 4 p.m. October 15 he was given a subcutaneous injection of 0.75 c.c. of the unheated and partially defibrinated blood obtained from Case II, 15½ hours previously, which had been kept 5½ hours in the refrigerator and 10 hours at room temperature. The earliest symptom, frontal headache, was complained of at 6 p.m., October 20, or at the expiration of 5 days and 2 hours after inoculation. . . The patient passed through a mild but typical attack, the temperature touching normal on the fifth day.

This case, therefore, serves as a "control" for the observations which are to follow, since it demonstrates that the blood drawn from the general circulation of Case II, at the beginning of the third day, contained the specific agent of yellow fever, and, in this respect, confirms the observations which have heretofore been reported by us.⁶

(b) The Partially Defibrinated Blood Heated for 10 Minutes at 55°C

Case IV

A.C., Spaniard, nonimmune, arrived at Habana, October 6, 1901. At 4.35 p.m., October 15, he was given subcutaneously 1.5 c.c. of the partially defibrinated blood which had been subjected to a temperature of 55°C. during 10 minutes. The specimen had been drawn from Case II, 16 hours before. The result of this injection was entirely negative, as the subject remained in perfect health during the 10 days following.

Case V

B.F.M., Spaniard, nonimmune, arrived at Habana, October 6, 1901. At 4.45 p.m., October 15, he received a subcutaneous injection of 1.5 c.c. of the same material that was used in Case IV. Result negative.

Case VI

S.O., Spaniard, nonimmune, arrived at Habana, October 7, 1901. At 4.50 p.m., October 15, he was given a subcutaneous injection of 1.5 c.c. of the same material that was used in Cases IV and V. No rise of temperature or other symptoms of ill health followed this injection.

We desire to invite attention to the fact that the four subjects whose protocols have been given above were young Spaniards who arrived at Habana at a time when yellow fever was not present in the city; that they were carried from the quarantine camp, at Tricornia, across the bay, direct to Columbia Barracks, near Quemados, Cuba, where they were kept for seven full days prior to inoculation; and that after inoculation they were kept under close daily observation for the future period of 10 days, during which time both temperature and pulse were recorded every third hour. Since under these circumstances each of the three nonimmunes (Cases IV, V, VI) received, without any disturbance to health, double the quantity of heated and partially defibrinated blood that sufficed when unheated to cause an attack of yellow fever in Case III, it follows that the specific agent present in the blood in yellow fever is destroyed, or, at least markedly attenuated, by a temperature of 55°C. maintained for 10 minutes.

(c) The Diluted and Filtered Serum

Case VII

P.H., American soldier, nonimmune, received at 11 a.m. October 15, 1901, a subcutaneous injection of 3 c.c. of the serum filtrate, representing 1.5 c.c. of the undiluted serum 10½ hours after the blood had been drawn from Case II. He remained in good health until 3 p.m. October 19, an interval of four days and four hours, when his face appeared flushed and his eyes somewhat injected. . . The patient was visited by the board of experts and the diagnosis of yellow fever confirmed. Examination of the dried blood for malarial parasites was negative. The patient recovered.

Case VIII

A.W.C., American soldier, nonimmune, was also given at 11.05 a.m. October 15, 1901, a subcutaneous injection of 3 c.c. of the diluted and filtered serum, being equivalent of 1.5 c.c. of the undiluted serum, 10½ hours after the blood had been drawn. He remained in his usual health until about noon, October 19, at which time he felt "out of sorts" and ate but little dinner. . . He was seen by the board of experts and his illness pronounced a typical case of yellow fever. Careful examination of the dried blood for malarial parasites was negative. The patient made a good recovery.

Case IX

J.R.B., American, nonimmune, at 2.30 p.m. October 15, 1901, was given a subcutaneous injection of 3 c.c. of the diluted

and filtered serum, equal to 1.5 c.c. of the undiluted serum. Fourteen hours had elapsed since the blood had been drawn from Case II.

This injection was followed by no symptoms of physical disturbance, until 3 p.m. October 19, an interval of four days and a half hour, when his temperature was 99.4°F., pulse 92. He complained of headache and flashes of heat, with slight pain between the shoulders, symptoms which, the subject stated, were quite unusual to him. At 9 p.m. temperature 98.4°F., pulse 84. There was no further febrile disturbance and the day following the subject was in his usual good health.

We thus observe that of 3 nonimmune individuals who received subcutaneously an injection of filtered blood serum derived from Case II of this report, 2 developed an unmistakable attack of yellow fever, after a period of incubation of 98½ hours and 100 hours respectively, while in 1 case the result must be regarded as negative.

As already stated, the serum used for these inoculations had been slowly filtered through a new Berkefeld laboratory filter. As soon as possible thereafter the filter was resterilized by steam and thoroughly tested as to its effectiveness in preventing the passage of bacteria. For this purpose a recent bouillon culture of *Staphylococcus pyogenes aureus* was used, of which 50 c.c. were passed through the filter. The filtrate thus obtained was transferred in quantities of 10 c.c. to each of the two flasks containing 200 c.c. of sterile bouillon, which were incubated at 37°C. for 4 days and thereafter kept at room temperature for 10 days longer, at the end of which time no growth had occurred. It appears, therefore, that the filter used for the filtration of the blood serum in Case II was to be relied upon for the delivery of a bacteria-free filtrate.

The production of yellow fever by the injection of blood serum that had previously been passed through a filter capable of removing all test of bacteria, is, we think, a matter of extreme interest and importance. The occurrence of the disease under such circumstances, and within the usual period of incubation, might be explained in one of two ways, viz, first, upon the supposition that the serum filtrate contains a toxin of considerable potency; or, secondly, that the specific agent of yellow fever is of such minute size as to pass readily through the pores of a Berkefeld filter.

In favor of the supposition that in yellow fever an active toxin is present in the blood may be cited the early and well-marked jaundice; the free hemorrhage from the mucous membranes of the mouth and stomach, doubtless due to profound changes in capillary vessel walls; the rapid progress of the disease to a fatal termination, the advanced fatty degeneration of the hepatic cells, as well as the marked parenchymatous changes found in the kidneys. If present in the blood this toxin would in all likelihood be found in the serum filtrate obtained from the blood, and if injected in sufficient quantity might induce an attack of yellow fever in a susceptible individual after the usual period of incubation. In this respect it would bear analogy to the incubation of this disease by the subcutaneous injection of a very small quantity of tetanus toxin, as reported by Nicolas⁷ in 1893, and more recently by Bolton, Fisch, and Walden.⁸

Against the view that a toxin is present in the serum filtrate, we invite attention to the innocuousness of the partially defibrinated blood when heated to 55°C. for 10 minutes, as shown

by the negative results in Cases IV, V, and VI. Here the toxin, which must have been present in just the same quantity as in the serum filtrate obtained from this blood, appears to have been completely destroyed by the temperature above mentioned. Now, although certain bacteria are destroyed by this temperature, as yet we know of no bacterial toxin that is rendered inert by such a low degree of heat continued for so short a time. The tetanus toxin, which has been found to be the most sensitive thus far requires, according to Kitasato, a temperature of 60°C. for 20 minutes, of 55°C. for 1½ hours, in order to destroy its activity.⁹

As a further test and in order to determine whether the serum filtrate contained something more particulate than a soluble toxin, we availed ourselves of the opportunity of observing the effect that would follow the transference to a third individual of blood drawn from one of the patients whose attack had been occasioned by the injection of 1.5 c.c. of serum filtrate (Case VII). If under these circumstances it would be found that the injection of a small quantity of blood was followed by an attack of yellow fever in a third individual, the evidence would point in the strongest manner to the presence of the specific agent of the disease in such blood, since we can hardly believe that a toxin which had undergone so great a dilution in the body of the second individual would still be capable of producing the disease.

Case X

October 22, 1901, 3 p.m., J.M.B., American, nonimmune, who on October 15, 1901, at 2.30 p.m., had been injected with 1.5 c.c. of serum filtrate with negative result (vide Case IX), and who still desired to have his immunity further tested, was, at the beginning of this, the eighth day after his former inoculation, given a subcutaneous injection of 1.5 c.c. of blood drawn from the venous circulation of Case VII early in the fourth day of the disease. At the time of inoculation the subjects' condition was quite normal. October 23, 3 p.m., after an incubation period of just 24 hours, he complained of frontal and slight basal headache and some pain between the shoulders. . . The case was seen by the board of experts and the diagnosis confirmed.

In considering this individual's attack, his infection must be attributed either to the injection of the serum filtrate derived from Case II, in which event the onset of his disease was postponed until the commencement of the ninth day after inoculation, or to the injection of blood obtained from Case VII, after a period of incubation of 24 hours.

In our own experience¹⁰ and that of Guit  ras¹¹ of 22 cases of experimental yellow fever, following the bite of the mosquito, in which the period of incubation was definitely and accurately ascertained, the longest period was 6 days and 1 hours, and the shortest period 2 days and 13 hours. If we take the cases produced by the injection of blood, 7 in number, exclusive of the case under consideration, the longest period was 5 days and 2 hours (Case III of this report) and the shortest 41 hours.

In view of these data, we believe we are justified in expressing the opinion that the source of infection in Case X must be attributed to the injection of blood drawn from Case VII, rather than to the injection of the filtered serum derived from the blood in Case II; and further, that the blood in Case VII contained the specific agent of yellow fever, which had, therefore, passed

through the filter along with the filtrate with which this latter individual had been inoculated.

The important questions which naturally arise from the foregoing experiments must be left for the future observations to determine.

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Exterior of the "Mosquito Building" at Camp Lazear. (Courtesy of the Walter Reed Army Institute of Research)

The Detachment Hospital Corps, Columbia Barracks, Cuba 1900

Historical Background: This photograph (Fig. 1) of the Detachment Hospital Corps was taken in September 1900 probably on the steps of the hospital at Columbia Barracks, Cuba. From the group of men pictured came those selected to make up the military garrison of Camp Lazear. In an address before the Medical and Chirurgical Faculty of the State of Maryland in April 1901, Walter Reed said these men were "personally selected by reason of former good conduct and interest in the work." Eight of these men volunteered for the yellow fever experiments, five of the eight developed yellow fever. Five additional members of the Detachment, not pictured, participated in the experiments, and four developed yellow fever. (Photograph courtesy of The Philip S. Hench Walter Reed Yellow Fever Collection, Historical Collections and Services, The Claude Moore Health Sciences Library, University of Virginia.)

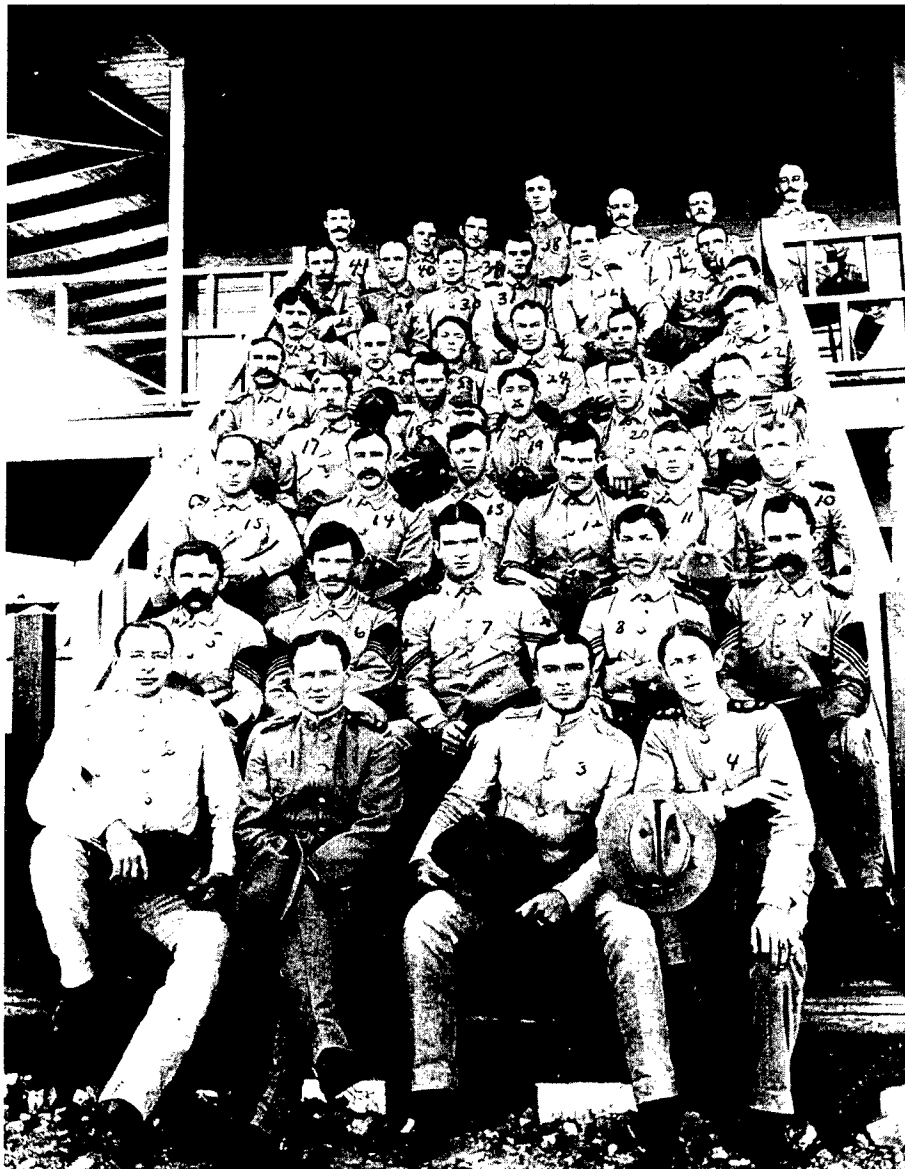


Fig. 1. Pictured in the photograph by number are: 1, 1st Lieutenant Albert E. Truby, Asst. Surgeon, U.S. Army; 2, Alva S. Pinto, Contract Surgeon; 3, Roul Amador, Contract Surgeon; 4, Robert P. Cooke, Contract Surgeon*; 5, A.H.S. Campbell; 6, A.H.S. Pahnke; 7, A.H.S. George Burton; 8, A.H.S. Cook; 9, A.H.S. Arnold; 10, Pvt. John R. Kissinger*; 11, Pvt. Braemer; 12, Pvt. Thomas Kane; 13, Pvt. De Lamar; 14, Pvt. Warren G. Jernegan*; 15, Pvt. John Morris; 16, Pvt. Lawrence; 17, Pvt. William Olsen*; 18, Pvt. Samillion; 19, Pvt. Carr; 20, Pvt. Martin; 21, Pvt. William McHardy; 22, Pvt. Gustave Lambert; 23, Pvt. Tate; 24, Pvt. Thomas M. England*; 25, Pvt. John E. Andrus*; 26, Pvt. Harroldsen; 27, Pvt. Fred G. West; 28, Pvt. Brent La Mar; 29, Pvt. James Tolar; 30, Pvt. Thomas Brault; 31, Pvt. Frank Buholtz; 32, Pvt. James Byington; 33, Pvt. William Williamson; 34, Pvt. Young; 35, Pvt. Springer; 36, Pvt. Rutledge; 37, Pvt. William Robertson; 38, Pvt. Courtney; 39, Pvt. Frank M. Dawley; 40, Pvt. Ed. Weatherwalks*; 41, Pvt. Charles G. Sontag*.

* Volunteered for yellow fever experiments. Yellow fever volunteers not pictured: Private Levi Folk, Private Wallace W. Forbes, Private James L. Hanberry, Private James Hildebrand, and Private Clyde L. West.

Historical Background: This article was published in the December 1915 issue of *The Scientific Monthly*. By that time, Dr. Agramonte was the sole surviving member of the 1900 Yellow Fever Board and was serving as professor of bacteriology and experimental pathology at the University of Havana. The article is the only first-hand account of the investigations written for a popular audience. Information not available elsewhere was revealed. Agramonte, believed to be immune to yellow fever because of his Cuban birth, allowed potentially infected mosquitoes to bite him just to feed them, despite the fact that he says he had no desire to test his immunity. He also discusses how he recruited and vetted Spanish immigrants for the study. Published 15 years after the Board first met in Cuba, Dr. Agramonte was able to provide perspective on the impact of the work. Initially, the Board's work was not universally accepted, but by 1915 its value was well known. The text of the article is presented unabridged. Several illustrations have been omitted.

The Inside History of a Great Medical Discovery

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The construction of the Panama Canal was made possible because it was shown that yellow fever, like malaria, could be spread only by the bites of infected mosquitoes.

The same discovery, which has been repeatedly referred to as the greatest medical achievement of the twentieth century, was the means of stamping out the dreaded scourge in Cuba, as well as in New Orleans, Rio de Janeiro, Vera Cruz, Colon, Panama and other cities in America.

This article is intended to narrate the motives that led up to the investigation and also the manner in which the work was planned, executed and terminated. No names are withheld and the date of every important event is given, so that an interested reader may be enabled to follow closely upon the order of things as they occurred and thus form a correct idea of the importance of the undertaking, the risk entailed in its accomplishment and how evenly divided was the work among those who, in the faithful performance of their military duties, contributed so much for the benefit of mankind; the magnitude of their achievement is of such proportions, that it loses nothing of its greatness when we tear away the halo of apparent heroism that well-meaning but ignorant historians have thrown about some of the investigators.

The whole series of events, tragic, pathetic, comical and otherwise, took place upon a stage made particularly fit by nature and the surrounding circumstances.

Columbia Barracks, a military reservation, garrisoned by some fourteen hundred troops, distant about eight miles from the city of Havana, the latter, suffering at the time from an epidemic of yellow fever, which the application of all sanitary measures had failed to check or ameliorate and finally, our experimental camp (Camp Lazear), a few army tents, securely hidden from the road leading to Marianao, and safeguarded, against intercourse with the outside world; the whole setting portentously silent and gloriously bright in the glow of tropical sunlight and the green of luxuriant vegetation.

Two members of a detachment of four medical officers of the U.S. Army, on the morning of August 31, 1900, were busily examining under microscopes several glass slides containing blood from a fellow officer who, since the day before, had shown symptoms of yellow fever; these men were Drs. Jesse W. Lazear and myself; our sick colleague was Dr. James Carroll, who presumably had been infected by one of our "experiment mosquitoes."

It is very difficult to describe the feelings which assailed us at that moment; a sense of exultation at our apparent success no doubt animated us; regret, because the results had evidently brought a dangerous illness upon our coworker and with it all associated a thrill of uncertainty for the reason of the yet insufficient testimony tending to prove the far-reaching truth which we then hardly dared to realize.

As the idea that Carroll's fever must have been caused by the mosquito that was applied to him four days before became fixed upon our minds, we decided to test it upon the first non-immune person who should offer himself to be bitten; this was of common occurrence and taken much as a joke among the soldiers about the military hospital. Barely fifteen minutes may have elapsed since we had come to this decision when, as Lazear stood at the door of the laboratory trying to "coax" a mosquito to pass from one test-tube into another, a soldier came walking by toward the hospital buildings; he saluted, as it is customary in the army upon meeting an officer, but, as Lazear had both hands engaged, he answered with a rather pleasant "Good morning." The man stopped upon coming abreast, curious no doubt to see the performance with the tubes, and after gazing for a minute or two at the insects he said: "You still fooling with mosquitoes, Doctor?" "Yes," returned Lazear, "will you take a bite?" "Sure I ain't scared of 'em," responded the man. When I heard this, I left the microscope and stepped to the door, where the short conversation had taken place; Lazear looked at me as though in consultation; I nodded assent, then turned to the soldier and asked him to come inside and bare his forearm. Upon a slip of paper I wrote his name while several mosquitoes took their fill; William H. Dean, American by birth, belonging to Troop B, Seventh Cavalry; he said that he had never been in the tropics before and had not left the military reservation for nearly two months. The conditions for a test case were quite ideal.

I must say we were in great trepidation at the time; and well might we have been, for Dean's was the first indubitable case of yellow fever about to be produced experimentally by the bite of purposely infected mosquitoes. Five days afterwards, when he came down with yellow fever and the diagnosis of his case was corroborated by Dr. Roger P. Ames, U.S. Army, then on duty at the hospital, we sent a cablegram to Major Walter Reed, chairman of the board, who a month before had been called to Washington upon another duty, apprising him of the fact that the theory of the transmission of yellow fever by mosquitoes, which

at first was doubted so much and the transcendental importance of which we could then barely appreciate, had indeed been confirmed.

State of Things Before the Discovery of Mosquito Transmission

Other infectious diseases, tuberculosis, for instance, may cause a greater death-rate and bring about more misery and distress, even to-day, than yellow fever has produced at any one time; but no disease, except possibly cholera or the plague, is so tragic in its development, so appalling in its action, so devastating in its results, nor does any other make greater havoc than yellow fever when it invades non-immune or susceptible communities.

For two centuries, at least, the disease has been known to exist endemically, that is, more or less continuously, in most of the Mexican Gulf ports, extending its ravages along the West India Islands and the cities of the Central and the South American coast.

In the United States it has made its appearance in epidemic form as far north as Portsmouth, N.H. At Philadelphia in 1793, more than ten per cent. of the entire population died of yellow fever. Other cities, like Charleston, S.C., suffered more than twenty epidemics in as many summers, during the eighteenth century. In the city of New Orleans, the epidemic, which developed in the summer of 1853, caused more than 7,000 deaths. Later, in 1878, yellow fever invaded 132 towns in the United States, producing a loss of 15,932 lives out of a total number of cases which reached to more than 74,000: New Orleans alone suffered a mortality of 4,600 at that time. Recently (1905), this city withstood what is to be hoped shall prove its last invasion, which, thanks to the modern methods employed in its suppression, based upon the new mosquito doctrine, only destroyed about 3,000 lives.

It is by contemplating this awful record, and much more there is which for the sake of brevity I leave unstated, that one realizes the boon to mankind, which the successful researches of the Army Board have proved. The work of prevention, the only one that may be considered effective when dealing with the epidemic diseases, was entirely misguided with regard to yellow fever until 1901: the sick were surrounded by precautions which were believed most useful in other infectious diseases, the attendants were often looked upon as pestilential, and so treated, in spite of the fact that evidence from the early history of the disease clearly pointed to the apparent harmlessness even of the patients themselves. All this notwithstanding, cases continued to develop, in the face of shotgun quarantine even, until the last non-immune inhabitant of the locality it had been either cured or buried.

The mystery which accompanied the usual course of an epidemic; the poison creeping from house to house, along one side of a street, seldom, crossing the road, spreading sometimes around the whole block of houses before appearing in another neighborhood, unless distinctly carried there by a visitor to the infected zone who himself became stricken, all this series of peculiar circumstances was a never-ending source of discussion and investigation.

In the year 1900; Surgeon H.R. Carter, of the then Marine Hospital Service, published a very interesting paper calling at-

tention to the interval of time which regularly occurred between the first case of yellow fever in a given community and those that subsequently followed; this was never less than two weeks, a period of incubation extending beyond that usually accorded to other acute infectious diseases. The accuracy of these observations has later been confirmed by the mosquito experiments hereinafter outlined.

Factors Which Led to the Appointment of the Board

One may well believe that such a scourge as yellow fever could not have been long neglected by medical investigators, and so we find that from the earliest days, when the germ-theory of disease took its proper place in modern science, a search for the causative agent of this infection was more or less actively instituted.

Men of the highest attainments in bacteriology engaged in numerous attempts to isolate the yellow fever microbe: unfortunately not a few charlatans took advantage of the dread and terror which the disease inspires, to proclaim their discoveries and their specific cures; one of these obtained wealth and honor in one of the South American republics for presumably having discovered the "germ" and prepared a so-called vaccination which was expected to eradicate the disease from that country, but for many years after the foreign population continued to suffer as before and the intensity and the spread of yellow fever remained unabated, although thousands of "preventive inoculations" were made every month.

Geo. M. Sternberg in 1880, then an army surgeon, was directly instrumental in exposing the swindle that was being perpetrated, putting an end, after the most painstaking investigation, to all the claims to discovery of the "germ" of yellow fever that had been made by several medical men in Spanish America. The experience which he obtained during a scientific excursion through Mexico, Cuba and South America gave him a wonderful insight as to the difficulties one has to contend with in such work and made him realize the importance of special laboratory training for such undertaking. It is interesting to note that, as surgeon general of the U.S. Army, twenty years after, General Sternberg chose and appointed the men who constituted the yellow fever board, in Cuba.

The year before the Spanish-American war, an Italian savant, who had obtained a well-deserved reputation as bacteriologist while working in the Institute Pasteur of Paris, came out with the announcement from Montevideo, Uruguay, that he had actually discovered the much-sought-for cause of yellow fever; his descriptions of the methods employed, though not materially different from those followed by Sternberg many years before, bore the imprint of truth and his experimental inoculations had apparently been successful. Sanarelli—that is his name—for about two years was the "hero of the hour," yet his claims have been proved absolutely false.

The question of the identity of his "germ" was first taken up by the writer under instructions from General Sternberg: during the Santiago campaign I had opportunity to autopsy a considerable number of yellow fever cases and, following closely upon Sanarelli's directions, only three times out of ten could his bacillus be demonstrated; at almost the same time, Drs. Reed and Carroll, in Washington, were carrying out experiments which showed that Sanarelli's bacillus belonged to the hog-

cholera group of bacteria and thus when found in yellow fever cadavers could play there only a secondary role as far as the infection was concerned.

Unfortunately, two investigators belonging to the U.S. Marine Hospital Service, Drs. Wasdin and Geddings, were, according to their claims, corroborating Sanarelli's findings: there was nothing to do but that the investigation should continue, and so I was sent by General Sternberg to Havana in December, 1898, with instructions and power to do all that might be necessary to clear up the matter. Wasdin and Geddings had preceded me; the work carried us through the summer of 1899; we frequently investigated the same cases; I often autopsied bodies from which we took the same specimens and made the same cultures, in generally the same kind of media, and finally we rendered our reports to our respective departments, Wasdin and Geddings affirming that Sanarelli's bacillus was present in almost all the cases, while I denied that it had such specific character and showed its occurrence in cases not yellow fever. A virulent epidemic which raged in the city of Santiago and vicinity during 1899 afforded me abundant material for research.

In the meantime the city of Havana was being rendered sanitary in a way which experience had taught would have overcome any bacterial infection, and, in fact, the diseases of filth, such as dysentery, tuberculosis, children's complaints and others, decreased in a surprising manner, while yellow fever seemed to have been little affected if at all.

Evidently, a more thorough overhauling of the matter was necessary to arrive at the truth, and while the question of Sanarelli and his claims was practically put aside, Surgeon-General Sternberg, recognizing the importance of the work before us and that its proportions were such as to render the outcome more satisfactory by the cooperation of several investigators in the same direction, wisely decided to create a board for the purpose and so caused the following to be issued:

Special Orders)
No. 122

HEADQUARTERS OF THE ARMY,
ADJUTANT GENERAL'S OFFICE,
WASHINGTON, MAY 24, 1900

Extract

34. By direction of the Secretary of War, a board of medical officers is appointed to meet at Camp Columbia, Quemados, Cuba, for the purpose of pursuing scientific investigations with reference to the infectious diseases prevalent on the Island of Cuba. Detail for the board:

Major Walter Reed, surgeon, U.S. Army;
Acting Assistant Surgeon James Carroll, U.S. Army;
Acting Assistant Surgeon Aristides Agramonte, U.S. Army;

Acting Assistant Surgeon Jesse W. Lazear, U.S. Army.
The board will act under general instructions to be communicated to Major Reed by the Surgeon General of the Army.

By command of MAJOR GENERAL MILES,
H. C. COBBIN,
Adjutant General

It may be of interest to the reader to learn who these men were and the reasons why they were probably selected for the work.

Major Reed, the first member in the order of appointment, was the ranking officer and therefore the chairman of the board. He was a regular army officer, at the time curator of the Army Medical Museum in Washington and a bacteriologist of some repute. He deservedly enjoyed the full confidence of the surgeon general, besides his personal friendship and regard. Reed was a man of charming personality, honest and above board. Every one who knew him loved him and confided in him. A polished gentleman and a scientist of the highest order, he was peculiarly fitted for the work before him.

Dr. James Carroll, the second member of the board, was a self-made man, having risen from the ranks through his own efforts: while a member of the Army Hospital Corps he studied medicine and subsequently took several courses at Johns Hopkins University in the laboratory branches. At the time of his appointment to the board he had been for several years an able assistant to Major Reed. Personally, Carroll was industrious and of a retiring disposition.

Dr. Jesse W. Lazear was the fourth member of the board. He had graduated from the College of Physicians and Surgeons (Columbia University) in the same class as the writer, in 1892, and had afterwards studied abroad and at Johns Hopkins. Lazear had received special training in the investigation of mosquitoes with reference to malaria and other diseases. Stationed at Columbia Barracks, he had been in Cuba several months before the board was convened, in charge of the hospital laboratory at the camp. A thorough university man, he was the type of the old southern gentleman, kind, affectionate, dignified, with a high sense of honor, a staunch friend and a faithful soldier.

The writer was the third member of the Army Board. Born in Cuba during the ten years' war, while still a child, my father having been killed in battle against the Spanish, I was taken to the United States and educated in the public schools and in the College of the City of New York, graduating from the College of Physicians and Surgeons in 1892. At the breaking out of the war I was assistant bacteriologist in the New York Health Department. The subject of yellow fever research was my chief object from the outset, and, at the time the board was appointed, I was in charge of the laboratory of the Division of Cuba, in Havana.

It may be readily seen from the brief sketch regarding the several members that the components of the yellow-fever board really constituted a perfectly consistent body, for the reason, mainly, that they were all men trained in the special field wherein their labors were to be so fruitful and that before their appointment to the board they had been more or less associated in scientific work.

First Part of the Work of the Board

My first knowledge of the existence of the board was had through the following letter from my friend Major Reed:

WAR DEPARTMENT,
SURGEON GENERAL'S OFFICE,
WASHINGTON, MAY 25, 1900

DR. A. AGRAMONTE,
Act'g Asst. Surgeon U.S.A.,
Military Hospital No. 1,
Havana, Cuba.

My dear Doctor: An order issued yesterday from the War Department calls for a board of medical officers for the investigation of acute infectious diseases occurring on the Island of Cuba. The board consists of Carroll, yourself, Lazear and the writer. It will be our duty, under verbal instructions from the Surgeon General, to continue the investigation of the causation of yellow fever. The Surgeon General expects us to make use of your laboratory at Military Hospital No. 1 and Lazear's laboratory at Camp Columbia.

According to the present plan, Carroll and I will be quartered at Camp Columbia. We propose to bring with us our microscopes and such other apparatus as may be necessary for the bacteriological and pathological work. If, therefore, you will promptly send me a list of the apparatus on hand in your laboratory, it will serve as a very great help in enabling us to decide as to what we should include in our equipment. Any suggestions that you may have to make will be much appreciated.

Carroll and I expect to leave New York, on transport, between the 15th and 20th of June and are looking forward, with much pleasure, to our association with you and Lazear in this interesting work. As far as I can see we have a year or two of work before us.

Trusting you will let me hear from you promptly, and with best wishes,

Sincerely yours,

(Signed) Walter Reed

On the afternoon of June 25, 1900, the four officers met for the first time in their new capacity, on the veranda of the officers' quarters at Columbia Barracks Hospital. We were fully appreciative of the trust and aware of the responsibility placed upon us and with a feeling akin to reverence heard the instructions which Major Reed had brought from the surgeon general; they comprised the investigation also of malaria, leprosy and unclassified febrile conditions, and were given with such detail and precision as only a man of General Sternberg's experience and knowledge in such matters could have prepared. After deciding upon the first steps to be taken, it was unanimously agreed that whatever the result of our investigation should turn out to be, it was to be considered as the work of the board as a body, and never as the outcome of any individual effort; that each one of us was to work in harmony with a general plan, though at liberty to carry out his individual methods of research. We were to meet whenever necessary, Drs. Reed, Carroll and Lazear to remain at the Barracks Hospital and I to stay in charge of the laboratory in

Havana, at the Military Hospital, where I also had a ward into which yellow-fever cases from the city were often admitted.

Work was begun at once. Fortunately for our purpose, an epidemic of yellow fever existed in the town of Quemados, in close proximity to the military reservation of Camp Columbia. Even before the arrival of Reed and Carroll, Lazear and I had been studying its spread, following the cases very closely; subsequently a few autopsies were made by me, Carroll making cultures from the various tissues and Lazear securing fragments for microscopical examination; a careful record was kept and the results noted; cases gradually became less in number as the epidemic slowly died out, about the middle of August.

In the meantime a rather severe outbreak of yellow fever had occurred in Santa Clara, a city in the interior of the island, having invaded the garrison and caused the death of several soldiers; as the origin of the infection was shrouded in mystery, and cases continued to appear among the troops even after they had moved out of the town, it was agreed that I should endeavor to trace the source of the epidemic and aid the medical authorities in establishing whatever preventive measures might seem proper. This service is here recorded because in the general discussion of the start and course of the epidemic with Dr. J. Hamilton Stone, the officer in charge of the military hospital, we incidentally spoke of the possible agency of insects in spreading the disease, pointing particularly in this direction the fact of the infection of a trooper who, suffering from another complaint, occupied a bed in a ward across the yard from where a yellow fever case had developed two weeks before.

The infection of the city of Santa Clara had evidently taken place from Havana, distant only one night's journey by train. Captain Stone, a particularly able officer, had already instituted effective quarantine measures before my arrival, so that I only remained there a few days.

But as to the actual cause of the disease we were still entirely at sea; it helped us little to know that a man could be infected in Havana, take the train for a town in the interior and start an outbreak there in the course of time.

Upon rejoining my colleagues (July 2) we resumed our routine investigations; not only in Quemados, where the disease was being stamped out, but also in Havana, at "Las Animas" Hospital and at Military Hospital No. 1, where my laboratory (the division laboratory) was located. There was no scarcity of material and the two members who until then had never seen a case of yellow fever (Reed and Carroll) had ample opportunity, and took advantage of it, to become acquainted with the many details of its clinical picture which escape the ordinary practitioner, the knowledge and the appreciation of which, in their relative value, give the right to the title of "expert."

Since the later part of June, reports had been coming to headquarters of an extraordinary increase of sickness among the soldiers stationed at Pinar del Rio, the capital of the extreme western province, and very soon the great mortality from so-called "pernicious malarial fever" attracted the attention of the chief surgeon, Captain A. N. Stark, who, after consulting with Major Reed, ordered me to go there and investigate. A man had died, supposedly from malaria, just before my arrival on the afternoon of July 19. The autopsy which I performed at once showed me that yellow fever had been the cause of his death, and a search through the military hospital wards revealed the

existence of several unrecognized cases being treated as malaria; a consultation held with the medical officer in charge showed me his absolute incapacity, as he was under the influence of opium most of the time (he committed suicide several months afterwards), and so I telegraphed the condition of things to headquarters; in answer I received the following:

CHIEF SURGEON'S OFFICE,
HDQRS. DEPT. HAVANA AND PINAR DEL RIO,
QUEMADOS, CUBA, JULY 20, 1900

SURGEON AGRAMONTE,
Pinar del Rio Barracks,
Pinar del Rio, Cuba

Report received last night. My thanks are due for your prompt action and confirmation of my suspicions.

STARK,
Chief Surgeon

Conditions in the hospital were such as to demand immediate action; the commander of the post refused to believe he had yellow fever among his 900 men and was loath to abandon his comfortable quarters for the tent life in the woods that I earnestly recommended. In answer to my telegram asking for official support, I received the following:

CHIEF SURGEON'S OFFICE,
HDQRS. DEPT. HAVANA AND PINAR DEL RIO,
QUEMADOS, CUBA, JULY 20, 1900

SURGEON AGRAMONTE,
Pinar del Rio Barracks,
Pinar del Rio, Cuba

Take charge of the cases. Reed goes on morning train. Wire for anything wanted. Nurses will be sent. Instructions wired commanding officer. Other doctors should not attend cases. Establish strict quarantine at hospital. You will be relieved as soon as an immune can be sent to replace you. Report daily by wire.

STARK,
Chief Surgeon

When Major Walter Reed came to Pinar del Rio (July 21) I had, the day before, established a separate yellow-fever hospital, under tents attended by some of the men who had already passed an attack and were thus immune. The Major and I went over the ground very carefully, we studied the sick report for two months back, fruitlessly trying to place the blame on the first case. I well remember how, as we stood in the men's sleeping quarters, surrounded by a hundred beds, from several of which fatal cases had been removed, we were struck by the fact that the later occupants did not develop the disease. In connection with this and particularly interesting, was the case of a soldier prisoner that had been confined to the guard-house since June 6; he showed the first symptoms of yellow fever on the twelfth and died on the eighteenth; none of the other eight prisoners in the same cell caught the infection, though one of them continued to sleep in the same bunk previously occupied by his dead comrade. More than this; the three men who had handled the

clothing and washed the linen of those who had died during the last month were still in perfect health. Here we seem to be in the presence of the same phenomenon remarked by Captain Stone in reference to his case at Santa Clara, and before that by several investigators of yellow fever epidemics; the infection at a distance, the harmless condition of bedding and clothing of the sick; the possibility that some insect might be concerned in spreading the disease, deeply impressed us and Major Reed mentions the circumstances in his later writings. This was really the first time the mosquito transmission theory was seriously considered by members of the board, and it was decided that, although discredited by the repeated failure of its most ardent supporter, Dr. Carlos J. Finlay, of Havana, to demonstrate it, the matter should be taken up by the board and thoroughly sifted.

The removal of the troops out of Pinar del Rio was the means of at once checking the propagation of the disease.

On the first day of August the board met and after due deliberation determined to investigate mosquitoes in connection with the spread of yellow fever. As Dr. Lazear was the only one of us who had had any experience in mosquito work, Major Reed thought proper that he should take charge of this part of the investigation in the beginning, while we, Carroll and I, continued with the other work on hand, at the same time gradually becoming familiar with the manipulations necessary in dealing with the insects.

A visit was now made to Dr. Finlay, who, much elated at the news that the board was about to investigate his pet theory, the transmission of yellow fever from man to man by mosquitoes, very kindly explained to us many points regarding the life of the one kind he thought most guilty and ended by furnishing us with a number of eggs which, laid by a female mosquito nearly a month before, had remained unhatched on the inside of a half empty bowl of water in his library.

Much to our disappointment and regret, during the first week of August, Major Reed was recalled to Washington that he might, in collaboration with Drs. Vaughan and Shakespeare, complete the report upon "Typhoid Fever in the Army." Thus we were deprived of his able counsel during the first part of the mosquito research. Major Reed was detained longer than he expected and could not return to Cuba until early in October, several days after Lazear's death.

The mosquito eggs obtained from Dr. Finlay hatched out in due time; the insects sent to Washington for their exact classification were declared by Dr. L.O. Howard, entomologist to the Agricultural Department, to be *Culex fasciata*. Later, they have been called *Stegomyia fasciata* and now go under the name of *Stegomyia calopus* (*Aedes cal.*).

Lazear applied some of these mosquitoes to cases of yellow fever at "Las Animas" Hospital, keeping them in separate glass tubes properly labeled, and every thing connected with their bitings was carefully recorded; the original batch soon died and the work was carried on with subsequent generations from the same.

The lack of material at Quemados caused us to remove our field of action to Havana, where cases of yellow fever continued to appear. We met almost every day at "Las Animas" Hospital, where Lazear was trying to infect his mosquitoes, or now and

then I performed autopsy upon a case, and Carroll secured sufficient cultures to last him for several days of bacteriological investigation.

Considering that, in case our surmise as to the insect's action should prove to be correct, it was dangerous to introduce infected mosquitoes among a population of 1,400 non-immunes at Camp Columbia, Dr. Lazear thought best to keep his presumably infected insects in my laboratory at the Military Hospital No. 1, from where he carried them back and forth to the patients who were periodically bitten.

Incidentally, after the mosquitoes fed upon the yellow fever patients, they were applied, at intervals of two or three days, to whoever would consent to run the risk of contracting yellow fever in this way; needless to say, current opinion was against this probability and as time passed and numerous individuals who had been bitten by insects which had previously fed upon yellow fever blood remained unaffected, I must confess that even the members of the board, who were rather sanguine in their expectations, became somewhat discouraged and their faith in success very much shaken.

No secret was made of our attempts to infect mosquitoes; in fact many local physicians became intensely interested, and Lazear and his tubes were the subject of much comment on the part of the Havana doctors, who nearly twenty years before had watched and laughed at Dr. Finlay, then bent apparently upon the same quest in which we were now engaged. Dr. Finlay himself was somewhat chagrined when he learned of our failure to infect any one with mosquitoes, but, like a true believer, was inclined to attribute this negative result more to some defect in our technique than to any flaw in his favorite theory.

Although the board had thought proper to run the same risks, if any, as those who willingly and knowingly subjected themselves to the bites of the supposedly infected insects, opportunity did not offer itself readily, since Major Reed was away in Washington and Carroll, at Camp Columbia, engrossed in his bacteriological investigations came to Havana only when an autopsy was on hand or a particularly interesting case came up for study. I was considered an immune, a fact that I would not like to have tested, for though born in the island of Cuba, I had practically lived all my life away from a yellow-fever zone; it was therefore presumed that I ran no risk in allowing mosquitoes to bite me, as I frequently did, just to feed them blood, whether they had previously sucked from yellow-fever cases or not. And so, time passed and several Americans and Spaniards had subjected themselves in a sporting mood to be bitten by the infected (?) mosquitoes without causing any untoward results, when Lazear applied to himself (August 16, 1900) a mosquito which ten days before had fed upon a mild case of yellow fever in the fifth day of his disease; the fact that no infection resulted, for Lazear continued in excellent health for a space of time far beyond the usual period of incubation, served to discredit the mosquito theory in the opinion of the investigators to a degree almost beyond redemption, and the most enthusiastic, Dr. Lazear himself, was almost ready to "throw up the sponge."

I had as laboratory attendant a young American, a private belonging to the Hospital Corps of the Army, who more than once had bared his arm to allow a weak mosquito a fair meal with which to regain its apparently waning strength; Loud, for that was his name, derided the idea that such a little beast could

do so much harm as we seemed ready to accuse it of, although he was familiar with the destruction caused by bacteria, but then, he used to say, "bacteria work in armies of more than a million bugs at the same time and no one would be d— fool enough to let more than one or two gnats sting him at once."

This state of things, the gradual loss of faith in the danger which mosquitoes seemed to possess, led Dr. Lazear to relax a little and become less scrupulous in his care of the insects, and often, after applying them to patients, if pressed for time, he would take them away with him to his laboratory at Columbia Barracks, where, the season being then quite warm, they could be kept as comfortably as at the Military Hospital laboratory. Thus it happened that on the twenty-seventh of August he had spent the whole morning at "Las Animas" Hospital getting his mosquitoes to take yellow-fever blood: the procedure was very simple; each insect was contained in a glass tube covered by a wad of cotton, the same as is done with bacterial cultures. As the mouth of the tube is turned downwards, the insect usually flies toward the bottom of the tube (upwards), then the latter is uncovered rapidly and the open mouth placed upon the forearm or the abdomen of the patient; after a few moments the mosquito drops upon the skin and if hungry will immediately start operations; when full, by gently shaking the tube, the insect is made to fly upwards again and the cotton plug replaced without difficulty. It so happened that this rather tedious work, on the day above mentioned, lasted until nearly the noon hour, so that Lazear, instead of leaving the tubes at the Military Hospital, took them all with him to Camp Columbia: among them was one insect that for some reason or other had failed to take blood when offered to it at "Las Animas" Hospital.

This mosquito had been hatched in the laboratory and in due time fed upon yellow-fever blood from a severe case on August 15, that twelve days before, the patient then being in the second day of his illness; also at three other times, six days, four days and two days before. Of course, at the time, no particular attention had been drawn to this insect, except that it refused to suck blood when tempted that morning.

After luncheon that day, as Carroll and Lazear were in the laboratory attending to their respective work, the conversation turning upon the mosquitoes and their apparent harmlessness, Lazear remarked how one of them had failed to take blood, at which Carroll thought that he might try to feed it, as otherwise it was liable to die before next day (the insect seemed weak and tired); the tube was carefully held first by Lazear and then by Carroll himself, for a considerable length of time, upon his forearm, before the mosquito decided to introduce its proboscis.

This insect was again fed from a yellow fever case at "Las Animas" Hospital on the twenty-ninth, two days, later, Dr. Carroll being present, though not feeling very well, as it was afterwards ascertained.

We three left the yellow-fever hospital together that afternoon; I got down from the doherty-wagon where the road forks, going on to the Military Hospital, while Carroll and Lazear continued on their way to Camp Columbia. On the following day, Lazear telephoned to me in the evening, to say that Carroll was down with a chill after a sea bath taken at the beach, a mile and a half from Camp, and that they suspected he had malaria; we therefore made an appointment to examine his blood together the following morning.

When I reached Camp Columbia I found that Carroll had been examining his own blood early that morning, not finding any malarial parasites; he told me he thought he had "caught cold" at the beach: his suffused face, blood-shot eyes and general appearance, in spite of his efforts at gaiety and unconcern, shocked me beyond words. The possibility of his having yellow fever did not occur to him just then; when it did, two days later, he declared he must have caught it at my autopsy room in the Military Hospital, or at "Las Animas" Hospital, where he had been two days before taking sick. Although we insisted that he should go to bed in his quarters, we could only get him to rest upon a lounge, until the afternoon, when he felt too sick and had to take to his bed.

Lazear and I were almost panic-stricken when we realized that Carroll had yellow fever. We searched for all possibilities that might throw the blame for his infection upon any other source than the mosquito which bit him four days before; Lazear, poor fellow, in his desire to exculpate himself, as he related to me the details of Carroll's mosquito experiment, repeatedly mentioned the fact that he himself had been bitten two weeks before without any effect there from and finally, what seemed to relieve his mind to some extent, was the thought that Carroll offered himself to feed the mosquito and that he held the tube upon his own arm until the work was consummated.

I have mentioned before that, as Lazear and I, vaguely hoping to find malarial parasites in Carroll's blood, sat looking into our microscopes that morning, the idea that the mosquito was what brought him down gradually took hold of our minds, but as our colleague had been exposed to infection in other ways, by visiting the yellow fever hospital "Las Animas," as well as the infected city of Havana, it was necessary to subject that same mosquito to another test and hence the inoculation of Private Dean, which is described in the opening chapter of this history.

Termination of the First Series of Mosquito Experiments

Death of Lazear

The month of September 1900, was fraught with worry and anxiety: what with Carroll's and Private Dean's attacks of yellow fever and Major Reed's inability to return, Lazear and I were well-nigh on the verge of distraction. Private Dean was not married, but Carroll's wife and children, a thousand miles away, awaited in the greatest anguish the daily cablegram which told them the condition of the husband and father, who was fighting for life, sometimes the victim of the wildest delirium caused by consuming fever, at others almost about to collapse, until one day, the worst of the disease being over, the wires must have thrilled at our announcement, "Carroll out of danger."

Fortunately both he and Dean made an uninterrupted recovery, but we were still to undergo the severest trial, a sorrow compared to which the fearful days of Carroll's sickness lose all importance and dwindle almost into insignificance.

On the morning of the eighteenth my friend and classmate Lazear, whom in spite of our short intercourse I had learned to respect and in every way appreciate most highly, complained that he was feeling "out of sorts." He remained all day about the officers' quarters and that night suffered a moderate chill. I saw him the next day with all the signs of a severe attack of yellow fever.

Carroll was already walking about, though enfeebled by his late sickness, and we both plied Lazear with questions as to the origin of his trouble; I believe we affectionately chided him for not having taken better care of himself. Lazear assured us that he had not experimented upon himself, that is, that he had not been bitten by any of the purposely infected mosquitoes.

After the case of Dean so plainly demonstrated the certainty of mosquito infection, we had agreed not to tempt fate by trying any more upon ourselves, and even I determined that no mosquito should bite me if I could prevent it, since the subject of my immunity was one that could not be sustained on scientific grounds; at the same time, we felt that we had been called upon to accomplish such work as did not justify our taking risks which then seemed really unnecessary. This we impressed upon Major Reed when he joined us in October and for this reason he was never bitten by infected mosquitoes.

Lazear told us, however, that while at "Las Animas" Hospital the previous Thursday (five days before), as he was holding a test-tube with a mosquito upon a man's abdomen, some other insect which was flying about the room rested upon his hand; at first, he said, he was tempted to frighten it away, but, as it had settled before he had time to notice it, he decided to let it fill and then capture it; besides, he did not want to move in fear of disturbing the insect contained in his tube, which was feeding voraciously. Before Lazear could prevent it, the mosquito that bit him on the hand had flown away. He told us in his lucid moments, that, although Carroll's and Dean's cases had convinced him of the mosquito's role in transmitting yellow fever, the fact that no infection had resulted from his own inoculation the month before had led him to believe himself, to a certain extent, immune.

How can I describe the agony of suspense that racked our souls during those six days? It seemed to us as though a life was being offered in sacrifice for the thousands which it was to contribute in saving. Across the span of thirteen years the memory of the last moments comes to me most vividly and thrilling, when the light of reason left his brain and shut out of his mind the torturing thought of the loving wife and daughter far away, and of the unborn child who was to find itself fatherless on coming into the world.

Tuesday, the twenty-fifth of September saw the end of a life full of promise: one more name, that of Jesse W. Lazear, was graven upon the portals of immortality. And we may feel justly proud for having had it, in any way, associated with our own.

The state of mind in which this calamity left us may better be imagined than described. The arrival of Major Reed several days after in a great measure came to relieve the tensivity of our nerves and render us a degree of moral support of which we were sorely in need.

Lazear's death naturally served to dampen our fruition at the success of the mosquito experiments, but, this notwithstanding, when the facts were known we were the subjects of much congratulation and the question whether the theory had been definitely demonstrated or not was the theme of conversation everywhere, about Havana and Camp Columbia particularly. We fully realize that these cases, two experimental and one accidental, were not sufficient proof, and that the medical world was sure to look with doubt upon any opinion based on such meager evidence; besides, in the case of Carroll, we had been

unable to exclude the possibility of other means of infection, so that we really had but one case, Dean's, that we could present as clearly demonstrative and beyond question. In spite of this we thought the results warranted their presentation in the shape of a "Preliminary Note," and after all the data were carefully collected from Lazear's records and those of the Military Hospital, a short paper was prepared which the Major had the privilege to read at the meeting of the American Public Health Association, held on October 24, in the city of Indianapolis.

For this purpose Major Reed went to the States two weeks after his return to Cuba, and Carroll also took a short leave of absence so as to fully recuperate, in preparation for the second series of inoculations which we had arranged to under take, after the Indianapolis meeting.

These inoculations, according to our program, were to be made upon volunteers who should consent to suffer a period of previous quarantine at some place to be selected in due time, away from any possibility of yellow fever.

It so happened then that I was left the only member of the board in Cuba and, under instructions from Major Reed, I began to breed mosquitoes and infect them, as Lazear used to do, wherever cases occurred, keeping them at my laboratory in the Military Hospital No. 1. Major Reed had also asked me to look about for a proper location wherein to continue the work upon his return.

Origin and Development of the Mosquito Theory

The possible agency of insects in the propagation of yellow fever was thought of by more than one observer, from a very early period in the history of this disease. For instance, Rush, of Philadelphia, in 1797, noticed the excessive abundance of mosquitoes during that awful epidemic. Subsequently, several others spoke of the coincidence of gnats or mosquitoes and yellow fever, but without ascribing any direct relation to the one regarding the other. Of course, man-to-man infection through the sole intervention of an insect was a thing entirely inconceivable and therefore unthought of until very recently, and in truth the discovery, as far as yellow fever is concerned, was the result of a slow process of evolution of the fundamental fact, taken in connection with similar findings, in other diseases.

The earliest direct reference is found in the writings of Dr. Nott, of Mobile, Ala., who in 1848 suggested that the dissemination of the yellow fever poison was evidently by means of some insect "that remained very close to the ground." But the first who positively pointed to the mosquito as the spreader of yellow fever, who showed that absence of mosquitoes precluded the existence of the disease and who prescribed the ready means to stamp it out, by fumigation and by preventing the bites of the insects, was Dr. Louis D. Beauperthuy, a French physician, then located in Venezuela. The writer has an original copy of his paper, published in 1853, where he fastens the guilt upon the domestic mosquitoes believing, in accord with the prevailing teachings of medical science that the mosquitoes infected themselves by contact or feeding upon the organic matter found in the stagnant waters where they are hatched, afterwards inoculating the victims by their sting. He recognized the fact that yellow fever is not contagious and therefore could not think of the possibility of man-to-man infection, as we know it today. The keenest observer was this man Beauperthuy, and, even at that

benighted time in the history of tropical medicine, made most interesting studies of the blood and tissues, employing the microscope and the chemical reactions in his research. No one believed him, and a commission appointed to report upon his views said that they were inadmissible and all but declared him insane.

This field of investigation remained dormant for a comparatively long period of time. Meanwhile another medical writer, Dr. Greenville Dowell, mentions in 1876, that "if we compare the effect of heat and cold on gnats and mosquitoes with yellow fever, it will be difficult to believe it is of the same nature, as it is controlled by the same natural laws." Soon after this, in 1879, the first conclusive proof of the direct transmission of a disease from man-to-man was presented by the father of tropical medicine, Sir Patrick Manson, with regard to filaria, a blood infection that often causes the repulsive condition known as elephantiasis and which the mosquito takes from man and after a short time gives over to another subject. This discovery attracted world-wide attention and many looked again toward the innumerable species of biting insects that dwell in the Tropic Zone, as a possible carrier of the obscure diseases which also prevail in those regions.

In 1881, Dr. Carlos Finlay, of Havana, in an exhaustive paper read before the Royal Academy of Sciences, gave as his opinion that yellow fever was spread by the bite of mosquitoes "directly contaminated by stinging a yellow fever patient (or perhaps by contact with or feeding from his discharge)." This latter view he held as late as 1900, which, though correct in the main fact of the transmission of the germ from a patient to a susceptible person by the mosquito, the *modus operandi*, as he conceived it, was entirely erroneous.

Dr. Finlay, unfortunately was unable to produce experimentally a single case of fever that could withstand the mildest criticism, so that at the time when the Army Board came to investigate the causes of yellow fever in Cuba, his theory, though practically the correct one, had been so much discredited, in a great measure by his own failures, that the best-known experts considered it as an ingenious, but wholly fanciful, one and many thought it a fit subject for humorous and sarcastic *repatee*. Finlay also believed, erroneously, that repeated bites of contaminated insects might protect against yellow fever and that the mosquitoes were capable of transmitting the germ to the next generation.

The wonderful discoveries of Theobald Smith, as to the agency of ticks in spreading Texas fever of cattle, and those of Ross and the Italian investigators who showed conclusively that malaria was transmitted by a species of mosquito, brought the knowledge of these various diseases to the point where the Army Board took up the investigation of yellow fever.

Second and Final Series of Mosquito Experiments

Major Reed came back to Havana in the early part of November, Carroll following a week after.

During their absence, I had been applying mosquitoes to yellow-fever patients at "Las Animas" Hospital, keeping them in my laboratory, as it was done at the beginning of the investigation; the season being more advanced, now and then a cold "norther" would blow and my insects suffered very much thereby, so that I had the greatest trouble in preventing their

untimely death: to this may be added the difficulty met in feeding them blood, for now that I knew their sting was dangerous, unto death perhaps, I could not allow any indiscriminate biting, but had to select for the purpose individuals who had suffered an attack of the disease and were therefore immune.

The necessity for an experimental camp became more imperative as time passed, not only where proper quarantine and isolation could be established, but also where the insects intended for the inoculations might receive better care. This entailed considerable expense.

Fortunately for us, the military governor of the island at that time, Brigadier General Leonard Wood, was a man who had received a thorough medical training; broad and clear-minded, he fully appreciated the importance of what might be the outcome of our researches. We found in him the moral support which we so much needed and, further he promptly placed at the disposal of the board sufficient funds with which to carry on the experiments to the end. I firmly believe that had other been the circumstances, had a more military and less scientific man been at the head of the government, the investigation would have terminated there and then, and many years would have passed, with hundreds of lives uselessly sacrificed, before we could have attained our present remarkable sanitary triumphs.

We immediately set about choosing a location for our camp. I had already looked over the ground, preferring the proximity of Camp Columbia, from where supplies could be easily obtained and because the Military Hospital there could be used for treating the cases that we intended to produce; I was therefore favorably impressed with the seclusion offered by a spot situated a short distance from the main road, in a farm, named San José, belonging to my friend Dr. Ignacio Rojas, of Havana. Major Reed decided upon this place after looking at many others in the neighborhood, so that on the twentieth of November we inaugurated our camp, which we named Camp Lazear, in honor to the memory of our dead colleague, consisting then of seven army tents, guarded by a military garrison, composed of men who had been carefully selected by virtue of their precious good record and their interest in the work to be undertaken.

Feeling that we had proved, to ourselves at least, the agency of the mosquito in yellow fever, it became our duty to disprove the theory, until then held as a certainty by many authorities, to the effect that the soiled bedding and clothing, the secretions and excreta of patients, were infectious and in some way carried the germ of the disease. We therefore designed a small wooden building, to be erected a short distance from the tents, with a capacity of 2,800 cubic feet. The walls and ceiling were absolutely tight, the windows and vestibule door screened and all precautions taken to prevent the entrance of insects.

Into this, called the "infected clothing building," three beds and a stove, to maintain a high tropical temperature, were introduced; also mattresses and pillows, underwear, pajamas, towels, sheets, blankets, etc., soiled with blood and discharges from yellow fever cases: these articles were put on the beds, hung about the room and packed in a trunk and two boxes placed there for the purpose.

The building was finished and equipped on November 30. That Friday evening, Dr. Robert P. Cook, U. S. Army, with two other American volunteers, entered it and prepared to pass the night: they had instructions to unpack the boxes and trunk, to

handle and shake the clothing and in every way to attempt to disseminate the yellow fever poison, in case it was contained in the various pieces. We watched the proceedings from the outside, through one of the windows. The foul conditions which developed upon opening the trunk were of such a character that the three men were seen to suddenly rush out of the building into the fresh air; one of them was so upset that his stomach rebelled; yet, after a few minutes, with a courage and determination worthy only of such a cause, they went back into the building and passed a more or less sleepless night, in the midst of indescribable filth and overwhelming stench.

The man who for a short time occupied the bed in room marked "3" became infected by the bites of mosquitoes previously introduced, while those, equally susceptible, who occupied beds W section marked "B" remained to good health. Only a wire-screen partition separated the two compartments.

For twenty consecutive nights these men went through the same performance; during the day they remained together, occupying a tent near their sleeping quarters. Dr. Cook, by voluntarily undergoing such a test, without remuneration whatsoever, proved his faith in the mosquito theory; his demonstration of the harmless character of so-called infected clothing, in yellow fever has been of the greatest importance. The other six men (two of them with Dr. Cook) who were subjected to this test, received each a donation of one hundred dollars for his services.

Many days even before the establishment of the experimental camp, the board had heard that several men who knew of our work were willing to submit to the inoculations and thus aid in clearing up the mystery of yellow fever. Two of these require special mention, John R. Kissinger, a private in the Hospital Corps of the Army, was the first to offer himself most altruistically, for, as he expressed it, his offer was made without any desire for pecuniary or other consideration and solely "in the interest of humanity and the cause of science," the other, J.J. Moran, a civilian employee, also stipulated as a condition that he was to receive no pay for his services. Both these men in due time, suffered from yellow fever and until very recently had never obtained any reward for the great risk which they ran so voluntarily and praiseworthy.

Kissinger, who after several years' service in the army became disabled, is receiving a pension from the government; Moran, I hope, is still well and in the employ of the Isthmian Canal Commission, justly enjoying the friendship and confidence of his superior officers. The names of Kissinger and Moran should figure upon the roll of honor of the U.S. Army.

On the day the camp was definitely organized, Kissinger, who had not gone outside the military reservation for more than a month, moved into Camp Lazear and received his first bite from a mosquito which evidently was not "loaded" for, again on November 23, he was stung by the same insect without result. On December 3, five mosquitoes were applied, which brought about a moderate infection in three days. Moran was also bitten by mosquitoes which were supposed to be infected on November 26 and 29, both times unsuccessfully. As will be seen, he was infected later on.

By this time we had decided, the weather having cooled considerably, that it was better to keep the mosquitoes at a higher temperature and nearer to the men who were to be inoculated: therefore it was planned to put up another small wooden struc-

ture, which was to be known as the "Mosquito Building" in which an artificial temperature could be maintained; at my suggestion, the building was so designed that it might serve to infect individuals; by liberating infected mosquitoes on the inside and exposing some person to their stings, we could try to reproduce the infection as we felt it occurred in nature. Another reason for the mosquito house was the need to obviate the transportation of the insects from the Military Hospital, where I kept them, to our camp, which could not be easily done without subjecting them to severe injury.

Upon one occasion I was taking four infected mosquitoes in the pocket inside my blouse from the laboratory in Havana to the experimental camp, accompanied by my attendant Private Loud; the horse which pulled my buggy, a rather spirited animal, becoming frightened at a steam roller, as we went around the corner of Colon Cemetery, started to race down the hill toward the Almendares River: Loud was thrown out by the first cavortings of the horse, who stood on its hind legs and jumped several times before dashing away, while I held tightly to the tubes in my pocket, as the buggy upset and left me stranded upon a sand pile in the middle of the road: the mosquitoes were quite safe, however, and upon my arrival at Camp Lazear I turned them over to Carroll for his subsequent care.

Another difficulty afterwards encountered was the scarcity of material susceptible to infection, for although several men had expressed a willingness to be inoculated, when the time came, they all preferred the "infected clothing" experiment to the stings of our mosquitoes. We then thought best to secure lately landed Spaniards, to whom the probable outcome of the test might be explained and their consent obtained for a monetary consideration. Our method was as follows; as soon as a load of immigrants arrived, I would go to Tiscornia, the Immigration Station across the Bay of Havana, and hire eight or ten men, as day laborers, to work in our camp. Once brought in, they were bountifully fed, housed under tents, slept under mosquito-bars and their only work was to pick up loose stones from the grounds, during eight hours of the day, with plenty of rest between. In the meantime, as the days of observation passed, I carefully questioned them as to their antecedents, family history and the diseases which they might have suffered; those who had lived in Cuba or any other tropical country before were discarded at once and also those who were under age or had a family dependent upon them. When the selection was finally made, the matter of the experiment was put to them. Naturally, they all felt more or less that they were running the risk of getting yellow fever when they came to Cuba and so were not at all averse to allow themselves to be bitten by mosquitoes: they were paid one hundred dollars for this, and another equal sum if, as a result of the biting experiment, they developed yellow fever. Needless to say, no reference was made to any possible funeral expenses. A written consent was obtained from each one, so that our moral responsibility was to a certain extent lessened. Of course, only the healthiest specimens were experimented upon.

It so happened that some reporter discovered what we were about, or perhaps some invidious person misrepresented the facts; at any rate, on the twenty-first of November a Spanish newspaper appeared with flaring headlines denouncing the American doctors who were taking advantage of the poor immi-

grants and experimenting with them by injecting all sorts of poisons! It called upon the Spanish consul to look after his subjects. In view of this we felt that if such campaign continued, in a short time it would either make it impossible to secure subjects or cause diplomatic pressure to be exerted against the continuance of our experiments. It was thought best to "beard the lion in his den" so the three of us called upon the consul the following day. He was surprised to hear one of us address him in his own language, having taken us all for Americans on first sight, and when I explained to him our method of procedure and showed him the signed contracts with the men, being an intelligent man himself, he had no objections to offer and told us to go ahead and not bother about any howl the papers might make.

The first three cases (two of them Spaniards) which we produced came down with yellow fever within a very short period, from December 8 to 13; it will therefore not surprise the reader to know that when the fourth case developed on December 15, and was carried out of the camp to the hospital, it caused a veritable panic among the remaining Spaniards, who, renouncing the five hundred pesetas that each had in view, as Major Reed very aptly put it, "lost all interest in the progress of science and uncontrollably severed their connection with Camp Lazear."

But there was a rich source to draw from, and the unexpected stampede only retarded our work for a short time. Our artificial epidemic of yellow fever was temporarily suspended while a new batch of susceptible material was brought in, observed and selected. The next case for that reason was not produced upon a Spaniard until December 30.

In the face of the negative experiments with supposedly contaminated articles, it rested with us to show how a house became infected and for this purpose the main part of the "mosquito building" was utilized.

This chamber was divided into two compartments by a double wire-screen partition, which effectually prevented mosquitoes on one side from passing to the other; of course there were no mosquitoes there to begin with, as the section of the building used for breeding and keeping them was entirely separated from the other, and there could be no communication between them.

On the morning of December 21, a jar containing fifteen hungry mosquitoes, that had previously stung cases of yellow fever, was introduced and uncovered in the larger compartment, where a bed, with all linen perfectly sterilized, was ready for occupancy. A few minutes after, Mr. Moran, dressed as though about to retire for the night, entered the room and threw himself upon the bed for half an hour; during this time two other men and Major Reed remained in the other compartment, separated from Moran only by the wire-screen partition. Seven mosquitoes were soon at work upon the young man's arms and face; he then came out, but returned in the afternoon, when five other insects bit him in less than twenty minutes. The next day, at the same hour of the afternoon, Moran entered the "mosquito building" for the third time and remained on the bed for fifteen minutes, allowing three mosquitoes to bite his hand. The room was then securely locked, but the two Americans continued to sleep in the other compartment for nearly three weeks, without experiencing any ill effects.

Promptly on Christmas morning Moran, who had not been

exposed to infection except for his entrance into the "mosquito building" as described, came down with a well-marked attack of yellow fever.

The temperature in this room, where these mosquitoes had been released, was kept rather high and a vessel with water was provided, where they might lay their eggs if so inclined, but notwithstanding all these precautions, it was subsequently found that the insects had been attacked by ants, so that by the end of the month only one of the fifteen mosquitoes remained alive.

It is hardly necessary to detail here how seven other men were subjected to the sting of our infected mosquitoes, of which number five developed the disease, but it may be interesting to note that two of these men had been previously exposed in the "infected clothing building" without their becoming infected showing that they were susceptible to yellow fever after all.

The evidence so far seemed to show that the mosquito could only be infected by sucking blood of a yellow-fever patient during the first three days of the disease: to prove that the parasite was present in the circulating blood at that time we therefore injected some of this fluid taken from a different case each time under the skin of five men: four of these suffered an attack of yellow fever as the result of the injection. The other one, a Spaniard, could not be infected either by the injection of blood or the application of mosquitoes which were known to be infected, showing that he had a natural immunity or more likely, that he had had yellow fever at some previous time.

While selecting the Spaniards, it was often ascertained that they had been in Cuba before, as soldiers in the Spanish army usually, and the natural conclusion was that they had undergone infection; it was very seldom that any escaped during the Spanish control of the island.

Thus terminated our experiment: with mosquitoes which, though necessarily performed on human beings, fortunately *did not cause a single death*; on the other hand, they served to revolutionize all standard methods of sanitation with regard to yellow fever. They showed the uselessness of disinfection of clothing and how easily an epidemic can be stamped out in a community by simple protecting the sick from the sting of the mosquitoes and by the extensive and wholesale destruction of these insects which, added to the suppression of their breeding places, if thoroughly carried out, are the only measures necessary to forever rid a country of this scourge.

Besides keeping a sharp lookout against the importation of yellow fever cases, these are the simple rules that have kept the Panama Canal free and prevented the slaughter of hundreds of foreigners, so generally expected every year, in former times.

Since we made our demonstration in 1901, our work has been corroborated by various commissions appointed for the purpose, in Mexico, Brazil and Cuba, composed variously of Americans, French, English, Cuban, Brazilian and German investigators. Nothing has been added to our original findings; nothing has been contradicted of what we have reported, and today, after nearly thirteen years, the truths that we uncovered stand incontrovertible; besides, they have been the means of driving out yellow fever from Cuba, the United States (Laredo, Texas, 1903 and New Orleans, La., 1905), British Honduras and several cities of Brazil.

Of the Army Board only I remain. Lazear, as reported, died during the early part of our investigations; Reed left us in 1902, and Carroll only five years later. The reader may wonder of what benefit was it to us, this painstaking and remarkable accomplishment which has been such a blessing to humanity! See what the late Surgeon General of the U.S. Army had to say in his report (Senate Document. 520, Sixty-first Congress, second session):

1. Major Walter Reed, surgeon, United States Army, died in Washington D.C., from appendicitis. November 23, 1902, aged 51. His widow, Emilie Lawrence Reed, is receiving a pension of \$125 a month.

2. Maj. James Carroll was promoted from first lieutenant to major by special act of Congress, March 9, 1907. He died in Washington, D.C., of myocarditis, September 10, 1907. His widow, Jennie H. Carroll, since his death, has received an annuity of \$125 a month, appropriated from year to year in the Army appropriation bill.

3. Dr. Jesse W. Lazear, contract surgeon. United States Army, died at Camp Columbia, Cuba, of yellow fever, September 25, 1900. His widow, Mabel M. Lazear, since his death, has received an annuity of \$125 a month appropriated from year to year in the Army appropriation bill.

4. Dr. Aristides Agramonte is the only living member of the board. He is professor of bacteriology and experimental pathology in the University of Habana and has never received, either directly or indirectly, any material reward for his share in the work of the board.

It is not for me to make any comments: the above paragraphs have all the force of a plain truthful statement of facts. Perhaps it is thought that enough reward is to be found in the contemplation of so much good derived from one's own efforts and the feeling it may produce of innermost satisfaction and in forming the belief that one had not lived in vain. In a very great measure, I know, the thought is true.

Historical Background: House Resolution 13060 was introduced by Congressman Jonathan M. Wainwright of New York on April 14, 1928 through the urging of James Peabody of the New York Biology Teachers Association. Their main goal seemed to be to provide assistance to many of these men who were in financial need. The original proposal called for a pension of \$250.00 per month for each named participant or their surviving family. It was amended by Congressman Harold Knutson of Minnesota to include a gold medal of "suitable emblems, devices, and inscriptions" and reduction of the monthly pension to \$125.00. Mr. Knutson said the purpose of his amendment was to equalize the pensions being paid to those who took part in the experiments or their widows. A photograph of the Congressional medal appears on the back cover of this supplement.

Public Law No. 858 (70th Congress), February 28, 1929

An Act To recognize the high public service rendered by Major Walter Reed and those associated with him in the discovery of the cause and means of transmission of yellow fever.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That in special recognition of the high public service rendered and disabilities contracted in the interest of humanity and science as voluntary subjects for the experimentations during the yellow-fever investigations in Cuba, the Secretary of War, be, and he is hereby, authorized and directed to publish annually in the Army Register a roll of honor on which shall be carried the following names: Walter Reed, James Carroll, Jesse W. Lazear, Aristides Agramonte, James H. Andrus, John R. Bullard, A. W. Covington, William H. Dean, Wallace W. Forbes, Levi E. Folk, Paul Hamann, James L. Hanberry, Warren G. Jernegan, John R. Kissinger, John J. Moran, William Olsen, Charles O. Sonntag, Clyde L. West, Doctor R. P. Cooke, Thomas M. England, James Hildebrand, and Edward Weatherwalks, and to define in appropriate language the part which each of these persons, played in the experimentations during the yellow-fever investigations in Cuba; and in further recognition of the high public service rendered by the persons hereinbefore named, the Secretary of the Treasury is authorized and directed to cause to be struck for each of said persons a gold medal with the Secretary of the Treasury, and to present the same to each of said persons as shall be living and posthumously to such representatives of

each of such persons as shall have died, as shall be designated by the Secretary of the Treasury. For this purpose there is hereby authorized to be appropriated, such amounts annually as may be necessary in order to pay to the following-named persons during the remainder of their natural lives the sum of \$125 per month, and such amount shall be in lieu of any and all pensions authorized by law for the following names persons: Private Paul Hamann; Private John R. Kissinger; Private William Olsen, Hospital Corps; Private Charles G. Sonntag, Hospital Corps; Private Clyde L. West, Hospital Corps; Private James Hildebrand, Hospital Corps; Private James A. Andrus, Hospital Corps; Mr. John R. Bullard; Doctor Aristides Agramonte; Private A.W. Covington, Twenty-third Battery, Coast Artillery Corps; Private Wallace W. Forbes, Hospital Corps; Private Levi E. Folk, Hospital Corps; Private James F. Hanberry, Hospital Corps; Doctor R. P. Cooke; Private Thomas M. England; Mr. John J. Moran, and the widow of Private Edward Weatherwalks.

Approved, February 28, 1929.

Public Law 858, 70th Congress was amended by Private Law 644, 84th Congress to include the name of Private Gustav E. Lambert and Public Law 85-879 to include the name of Dr. Roger P. Ames. Of the Army doctors in Cuba, Dr. Ames, a contract surgeon, was considered the most expert clinician in caring for yellow fever and cared for all the volunteers who became ill. Private Lambert was his most trusted and competent corpsman.

Epilogue: The U.S. Army Yellow Fever Board of 1900

After the early discoveries of the Yellow Fever Board at Camp Lazear, General Leonard Wood issued General Order No. 6 on December 21, 1900. This order set measures to be used for mosquito control on all U.S. Army posts in Cuba and was ultimately applied to the civilian population as well. In 1899–1900 despite Havana being “cleaned up” by the Sanitary Corps of the U.S. Army, there were still over 300 deaths from yellow fever.¹

Major William Crawford Gorgas, the Chief Sanitation Officer of Havana, was not convinced that the mosquito was the main agent of yellow fever transmission. Although he believed the results of the Yellow Fever Board's experiments he said, “I myself had seen the work and was convinced that the mosquito could convey yellow fever, but I was hardly prepared to believe that it was the only way, or even the ordinary way, of conveying the disease.”²

Following approval of higher headquarters, the mosquito control work began in Havana in February 1901 and under Gorgas was “pushed in every direction.” The U.S. Army launched one of its most successful “wars” ever, war against the mosquito. Results were almost immediate, cases and deaths both decreased dramatically. The yellow fever scourge was essentially stopped in its deadly tracks. There were 12 deaths in January and February 1901 in Havana, and starting in March, the first full month of mosquito clean-up campaign, there were only six the rest of the year. From September 1901 until July 1902 there was not even a single case.² Yellow fever had been constantly present in Havana for 150 years and was essentially wiped out in less than 150 days. The world was astounded by the results.

Major Jefferson Randolph Kean and other friends of Walter Reed campaigned for him to succeed George Miller Sternberg as Surgeon General of the Army but apparently he was never seriously considered. In June 1902, COL William H. Forwood was named to succeed Sternberg. Later that same month, Reed received two honorary degrees, an L.L.D. from the University of Michigan, honoring “Walter Reed, most eminent physician, famous for his investigations of the causes of diseases” and an M.A. from Harvard, “Walter Reed, graduate of the University of Virginia, the army surgeon who planned and directed in Cuba the experiments which have given man control over that fearful scourge yellow fever.”

By the fall of 1902 it was clear that his health was suffering. On the first of November he became the librarian of the Surgeon General's Library, a position he had wanted for several years but would hold only 23 days. After work on November 12th, he was unable to teach his evening class. Two days later on Friday, he thought he had appendicitis and was seen by Major William Borden, his friend and Commander of the Army Hospital at Washington Barracks (now Fort Leslie J. McNair).

Major Borden agreed and they discussed the possibility of operating the following week. Reed went home and by Sunday was actually feeling better and able to receive friends that afternoon. His temperature went up Sunday night and the next day he was taken to the hospital and operated on by Major Borden. Borden was dismayed at what he found, saying that Reed's symptoms “in no way indicated the gravity of the . . . trouble.”³

There was hope for several days that he might recover but peritonitis developed; in this pre-antibiotic era, it was futile.

At the time of Reed's illness, the Secretary of War had stated in his annual report, still in press, that Reed would, by law, become a Lieutenant Colonel within a few months. The Secretary also said that he would ask the President to authorize Reed's appointment to Assistant Surgeon General with the rank of Colonel.⁴ Neither promotion nor recognition came to him. Walter Reed, 51, died in the early hours of November 23, 1902.

Walter Reed was buried in section number three of Arlington National Cemetery. His wife Emilie survived him by 48 years. She continued to live in Washington, DC and was buried beside her husband when she died in 1950. Their son Lawrence, who had enlisted in the Army during the Spanish-American War and was serving in Cuba when his father arrived in June 1900 to begin his experiments, remained in the Army for over 40 years and retired as a Major General. Lawrence Reed who served as The Inspector General of the Army from 1935 to 1939 died at Walter Reed Army Medical Center in 1956. Walter Reed's daughter, Blossom, was living in Pennsylvania when she died in 1964. Both are buried in Arlington National Cemetery.

Dr. James Carroll, second in charge of the commission after Reed, voluntarily participated in the early yellow fever experiments. Forty-six years old at the time and married with 5 children, he knew as did the others that mortality of yellow fever rapidly increased with age. He developed a very severe case and although not diagnosed at the time, he probably suffered with the complication of cardiac damage. His damaged heart continued to plague him for the remainder of his life.

Carroll despite his long enlisted service prior to the Spanish-American War, served as a Contract Surgeon during his work with the Yellow Fever Commission. After the successes of the Board, Generals Wood and Sternberg recommended that Carroll be promoted to Major but this was denied due to a moratorium on promotions. He applied for and received a Regular Army Commission as First Lieutenant in late 1902 and later served, after Reed's death, as Curator of the Army Medical Museum. He wrote widely on yellow fever in national and international journals. He also spoke at many national meetings and became a jealous guardian of the historical accounts of the commission's work. His last publication was the chapter on yellow fever in William Osler's *Systems of Medicine*.

Carroll was finally promoted by Special Act of Congress from First Lieutenant to Major on March 9, 1907. He died in Washington, DC on September 16, 1907 possibly from complications of valvular heart disease brought on by his experimental case of yellow fever. He was 54. Carroll was also buried in Arlington National Cemetery. A bronze plaque in his memory was placed at the University of Maryland Medical School in Baltimore and during World War II a liberty ship, built by Bethlehem-Fairfield Shipyard in Baltimore, was named in his honor in November 1943.

Aristides Agramonte, who had also served the commission as a Contract Surgeon, remained in his native Cuba. He became a Professor of Bacteriology and Experimental Pathology at the

University of Havana. At the time of his death in 1931, he was Professor of Tropical Medicine at Louisiana State University in New Orleans.

Jesse Lazear died from yellow fever in September 1900 during the early phases of the work of the Yellow Fever Board. His acquisition of yellow fever remains a mystery. He was buried in #138 Temporary Government Cemetery on the road between La Plaza and Quemados, Cuba. The following year he was re-interred in Loudon Park Cemetery, Baltimore.

In 1902, Battery "Lazear" was named in his honor at Fort Howard, Maryland, an active U.S. Army post until 1940. In 1904 a memorial plaque was placed at the Johns Hopkins University Medical School in Baltimore where speakers included Drs. William Welch, W.S. Halsted, and William Osler. In 1940 the Jesse W. Lazear Chemistry Hall was dedicated at Washington and Jefferson College in Washington, Pennsylvania. Dr. Philip S. Hench was asked to speak at this dedication and in preparing for his presentation became fascinated with the work of the U.S. Army Yellow Fever Board. He spent the remainder of his life collecting artifacts to include books, articles, letters and photographs related to the work of the Board. Following his death in 1965, this large collection was given to the University of Virginia and is housed in the Claude Moore Health Sciences Library. The University of Virginia displays many of these materials on its extensive web site at: www.med.virginia.edu/hour-library/historical/yelfev

Dr. Carlos Finlay had publicly proposed in 1881 that the female *Culex* mosquito was "the intermediate agent in the transmission of yellow fever." Finlay who had been unable to prove it and had been derisively called by some "the mosquito man," became the toast of Havana. He was praised and feted around the country and the world. He received international recognitions and appointments to various boards and associations. Finlay died in Havana at age 82 in 1915.

Major William C. Gorgas was promoted to Colonel after the tremendous success of his mosquito eradication program in Havana. He worked his same sanitary magic several years later in Panama greatly assisting in the completion of the Panama Canal. He served as Surgeon General of the U.S. Army from 1914 to 1918. The recently deactivated U.S. Army Hospital in Panama honored his name.

General Leonard Wood was the Governor General of Cuba who provided financial and command support for the work of the Yellow Fever Board. He ultimately became Chief of Staff of the U.S. Army (1910-1914) and was an unsuccessful candidate for the Republican Presidential nomination in 1920. He served

as Governor General of the Philippines from 1921 until 1927. Fort Leonard Wood in Missouri and its hospital, the General Leonard Wood U.S. Army Hospital, memorialize his name.

The first Nobel Prize for Physiology or Medicine was awarded in 1901. Sir Ronald Ross won the prize in 1902 for his discovery that malaria is transmitted by mosquitoes. Walter Reed's death made him ineligible, as Alfred Nobel had specified in his will that the awards not be given posthumously. There were several campaigns for the surviving members of the Yellow Fever Board to receive the prize but this did not happen. Fifty years after the Yellow Fever Board completed its work, the 1951 Nobel Prize did go to someone working in the yellow fever field, Dr. Max Theiler of the Rockefeller Institute. He led the development of the 17 D yellow fever vaccine, still in use today.

The accomplishments of the 1900-1901 U.S. Army Yellow Fever Board and the enlisted soldiers that assisted and volunteered for their experiments are truly extraordinary. Incalculable contributions to the Army, the nation, and the world were made by the application of their discoveries concerning the transmission of yellow fever. A centuries-old, dreaded, and fearful scourge was quickly controlled and essentially eradicated. They were the first to show experimental transmission of a viral disease from man to man. They were the first research group to get informed consent from their experimental subjects, setting a new standard for the ethical clinical research. They were also incredibly fortunate, for neither the brilliance of their thoroughness nor the genius of their experimental design could have bequeathed them the extraordinary luck they had, for not a single one of their volunteers died.

Dr. Henry Rose Carter wrote in a letter concerning their discoveries "Few scientific discoveries — medical or otherwise — are in their entirety the work of any one man. He who puts the capstone on the completed structure gets — as he should — the credit for it, but the foundation and walls may — and generally have been — built by many hands."⁵

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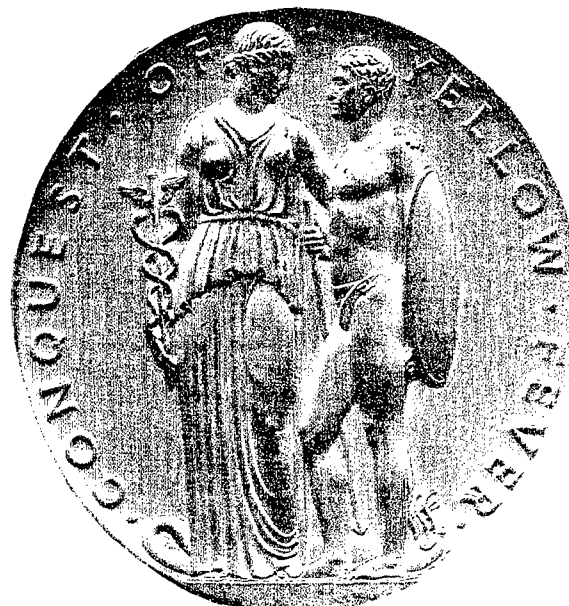
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Authorized by act of Congress in 1929, the gold medal, sixty-three millimeters in diameter, was designed and sculpted by Mr. Thomas Hudson Jones of the Institute of Heraldry. It shows two figures standing, the first representing Hygenia, the ancient goddess of health, garbed in a classic tunic, holding in her right hand the staff of Mercury (caduceus) and with her left arm in the gesture of protection of the soldier on the right who bears a lance and shield (right). The soldier represents the men who volunteered for the yellow fever experiments. At their feet in the background is a figure of pestilence, defeated. Around the perimeter, the words "Conquest of Yellow Fever."

On the reverse side (below) around the top are the words "The Congress of the United States, Act of February 28, 1929." Centered in the middle are the words "Awarded To" and below, a tablet for the name of the recipient to be engraved. Below the tablet are the words "In recognition of the high public service of Major Walter Reed, USA and associates who gave to man control of yellow fever." (Image courtesy of The Philip S. Hench Walter Reed Yellow Fever Collection, Historical Collections and Services, The Claude Moore Health Sciences Library, University of Virginia.)



The following twenty-four men or their families were awarded the medal:

Walter Reed	Levi E. Folk
James Carroll	Paul Hamann
Jesse W. Lazear	James L. Hanberry
Aristides Agramonte	James Hildebrand
James H. Andrus	Warren G. Jernegan
Roger P. Ames	John R. Kissinger
John R. Bullard	Gustaf E. Lambert
Robert P. Cooke	John J. Moran
A. W. Covington	William Olsen
William H. Dean	Charles O. Sonntag
Thomas M. England	Edward Weatherwalks
Wallace W. Forbes	Clyde L. West