Solving Yellow Fever Riddle Took Years of International Collaboration

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How will COVID-19 end? Decisively, with a vaccine, or slowly, with herd immunity? Will it downshift to a recurring nuisance and a manageable condition? Or will we see an amalgam of endgames, varying by time and place?

Perhaps New Orleanians 150 years ago pondered similar questions about the dreaded pestilence of their era, yellow fever. Though it plagued the region repeatedly since the late 1700s, and elsewhere since the 1600s, the basic causes of the disease remained largely a mystery into the late 1800s. Most researchers theorized at the time that moisture, heat and decaying organic matter gave rise to yellow fever, and that in New Orleans, such noxious "miasmas" emanated principally from swamps and marshes.

In 1834, seven physicians organized the Medical College of Louisiana to train young doctors in treating yellow fever, cholera, malaria, smallpox and other diseases. A success, the private college shifted to state control as the University of Louisiana in 1847, and soon developed an impressive campus on the present-day 900 block of Common Street.

That same summer, 2,600 people perished in the latest yellow fever epidemic, the worst to date. That figure more than tripled during the summer of 1853, the worst in New Orleans history, when 7,849 died. Another 5,000 lost their lives over the two subsequent summers, followed by 4,855 in 1858, the second-worst in the city's history. Official figures were all likely undercounts of actual deaths, possibly by wide margins. By comparison, the coronavirus pandemic had claimed the lives of about 550 New Orleanians to date, in a city population two to three times larger than it was in the 1850s

The epidemics of the 1850s motivated a wave of new research from the doctors of the University of Louisiana and at the Board of Health, which had appointed a Sanitary Commission to study the 1853 outbreak. Those efforts, led by Dr. Edward Hall Barton, used more sophisticated statistical methods to tease out relationships among weather conditions, standing water, soil-disturbance events, and the chronology of yellow fever cases and deaths.

Their meticulous graphs and tables bear a haunting semblance to the sort of daily COVID-19 data reports we've all become accustomed to seeing since March.

Barton and his colleagues were clearly on to something about yellow fever — there was some sort of relationship to stagnant water and poor urban sanitation. But the doctors could not quite pinpoint the causative factor, or the mechanism of spread. Was yellow fever contagious person to person? From environment to person? From the dead to the living?

Those basic questions remained unanswered 20 years later, when the Yellow Fever Epidemic of 1878 killed as many as 20,000 people throughout the Mississippi Valley, including 5,000 in Memphis, 4,056 in New Orleans, and 3,200 in Mississippi.

While the scourge appears to have spread domestically from New Orleans, it probably arrived here from Havana, Cuba, which over the centuries had endured relentless yellow fever plagues.

The disease being endemic to both cities, the U.S.-Havana Yellow Fever Commission decided in 1879 to unite researchers from New Orleans with their counterparts in the contested Spanish colony of Cuba. Getting the international experts in the same room would allow them to share experiences, compare notes, debate theories, and possibly collaborate on a solution.

Chairing the commission was Dr. Stanford Emerson Chaillé, a physiologist with the University of Louisiana School of Medicine, who brought along a medical student named Rudolph Matas, a Louisianian of Catalonian descent.

In Havana, the delegates met a commanding figure by the name of Dr. Carlos Juan Finlay, a 46-year-old Franco-Scot-Cuban scientist whom Matas later described as "the model of exemplary wisdom, of the laborious worker wealthy in strength of knowledge, in rectitude of principles, in conscientiousness and intellectual integrity."

Finlay had been studying yellow fever in Cuba since the early 1860s, and his more recent work seemed to subvert the conventional wisdom. Yes, urban sanitation was important, for various health reasons. But did urban filth and stagnant water actually *cause* yellow fever? "Sanitary measures generally adopted to prevent the spread of yellow fever," wrote Dr. Juan A. Del Regato, himself a famed Cuban physician, actually "were inconsistent with a number of observed facts."

Carlos Finlay, courtesy Wikipedia Commons.

From Chaillé's pioneering work in New Orleans in the use of microscopic methods, Finlay gleaned the idea to examine tissue and lesions from yellow fever victims. What Finlay found led him to doubt that insalubrious vapors or "miasmas" played any role.

Finlay thus surmised that some independent vector was at work, something affiliated with poor urban sanitation that could also tap human blood vessels — "all of which conditions," Finlay later wrote, "the mosquito satisfied most admirably through its bite."

In 1880, according to an article by Dr. Enrique Chaves-Carballo in the journal *Military Medicine*, Finlay began his scientific testing. He chose to start with the *Culex* species, which was known to lay eggs in puddles and flourish in dense urban environments. Determining that it was the female that sucked blood, Finlay and his assistant, Dr. Claudio Delgado, carefully harvested their eggs, hatched and nurtured the larvae to maturity, and exposed them to a human infected with yellow fever to obtain blood meals.

Now came the experiment. Having secured "necessary authorization" from the Spanish military to recruit 20 volunteer soldiers for the study, Finlay designated 15 to serve as experimental controls, and subjected the other five to the female *Culex* that had bitten the yellow fever victim.

"The first experimental subject," wrote Chaves-Carballo, "was Francisco Beronat, a 22-year-old Spanish soldier, who was inoculated on June 30, 1881. Nine days later, he developed fever, jaundice, and albuminuria." Beronat soon recovered, and Finlay came away sensing he had found the likely culprit.

He wrote up his findings and, on Aug. 14, 1881, presented “The Mosquito Hypothetically Considered as the Agent of Transmission of Yellow Fever” to the prestigious Spanish Royal Academy of Medical, Physical and Natural Sciences at its meeting in Havana.

The response to Finlay’s mosquito hypothesis was devastating. It was greeted with “incredulity and ridicule” from his peers, who wholly rejected it. And so the medical establishments in Cuba and the U.S. returned to their entrenched theories regarding sanitation and miasmas, and thousands more would perish to yellow fever in the years to come.

Finlay, disappointed but undaunted, continued with his research, refining his hypothesis. Two Southern doctors, Matas, of Louisiana and William Gorgas of Alabama, advocated for Finlay’s work, keeping his ideas circulating in the medical discourse.

By the late 1890s, the U.S. had more direct interests in the Caribbean basin. Tropical fruit firms increasingly invested in the region; imperialist strains within the U.S. government eyed possible island colonies; and there was talk of constructing a canal across the Central American isthmus.

In 1898, war broke out with Spain, and more U.S. soldiers would die of tropical diseases in Cuba than in the ensuing battles.

In 1900, the U.S. Army Fourth Yellow Fever Commission launched under the leadership of Maj. Walter Reed, and once again, American doctors set off to meet with their peers in Cuba, now on the path to independence following Spain’s defeat in the Spanish-American War.

The commissioners’ first stop in Havana? 110 Aguacate Street, home to Carlos Juan Finlay, now 67 and still busy with his mosquito experiments. Apparently his American advocates had succeeded in keeping his name and research alive, in the wake of that 1881 humiliation.

The right people were finally in the same room — literally. “Finlay was elated,” wrote Chaves-Carballo, “and regaled the visitors with a detailed exposition of his ideas, reprints of his publications, experimental notes, and documents related to his work.” Finlay also showed them the eggs of the *Culex* mosquito, which an entomologist on the team confirmed to be *Culex fasciatus.*

Now edified with Finlay’s findings, the commissioners got to work with their own experiments at Quemados, Cuba, where an epidemic had been breaking out.

Things got off a rough start. One team member became infected by a trial *Culex* and became severely ill; another got bitten by a wild *Culex* and later died. But under Reed’s guidance, the commissioners were able to conduct critical tests and take a host of tissue, blood, and organ samples, which Reed analyzed with the latest methods, in Cuba and in his lab in Washington. Reed was able to prove scientifically that *Culex fasciatus* was indeed the vector of the virus that caused yellow fever.

On Oct. 23, 1900, Reed presented his findings at the American Public Health Association’s annual meeting in Indianapolis. He shared authorship of the paper, “The Etiology of Yellow Fever — a Preliminary Note,” with his colleagues James Carroll, A. Agromonte, and Jesse Lazear, pointing out that Lazear had died of the very disease he helped solve.

He acknowledged that the mosquito hypothesis had been “first advanced and ingeniously discussed by Dr. Carlos J. Finlay,” to whom the commission wished to “express our sincere thanks” for his critical research on

"yellow fever during the past nineteen years." Reed also acknowledged the role of Italian researchers in their similar efforts to understand malaria; of U. S. Marine Hospital Service researchers in studying outbreaks in Mississippi; and of the work of Liverpool School of Tropical Medicine in England.

Vaccines for yellow fever were later developed during the 1910s through 1940s through research spanning from Japan to Brazil to France — truly an international multidisciplinary collaboration.

Alas, for New Orleans, there would be one more epidemic, in 1905, which claimed the lives of over 400 people. Cities by this time were swiftly developing vector-control campaigns to spray mosquitoes, reduce breeding habitat, and improve urban sanitation. The 1905 outbreak, centered around the lower French Quarter, would prove to be the last major yellow fever plague in the United States.

The heroes of this story live on through their accomplishments. Finlay is a national hero in Cuba today, known to every schoolchild. Reed had long been honored in the name of the U.S. Army's flagship hospital in Washington, D.C., and more recently in the U.S. Department of Defense's Walter Reed Army Institute of Research.

Chaillé, chair of the 1879 U.S.-Havana Yellow Fever Commission, went on to became known as the "Father of Hygiene and Health Education" and dean of the University of Louisiana School of Medicine. In 1884, that institution became Tulane University of Louisiana, and its School of Medicine today is the proud home of the Rudolph Matas Library of Health Sciences. Gorgas, the Alabamian who with Matas kept Finlay's work alive, went on to establish mosquito-control campaigns in Florida, Cuba, and Panama, saving thousands of lives.

As for *Culex fasciatus,* that invasive mosquito species was later classified as *Stegomyia fasciata*, and is now known as *Aedes aegypti.* It's still rife in New Orleans today, the vector of Zika, and if you're reading this article anywhere in the southeastern U.S., you've probably been bitten by *Aedes aegypti.*

Yellow fever is still with us too. The World Health Organization considers the disease to be endemic to certain African and Latin American countries, and while epidemics are now rare, some 200,000 cases and 30,000 deaths occur annually.

Amid the current pandemic, it's worth remembering that resolving the yellow fever riddle took many years and many experts from various disciplines and countries working together. It saw centuries wasted on archaic theories, and another 19 years lost to a mistakenly rejected hypothesis.

Yellow fever did not end decisively, nor did it downgrade to a mere nuisance. To this day, it takes constant effort on many fronts — vector control, public sanitation, immunization, health care — to keep humanity's eventual victory over yellow fever from becoming any more costly.

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