

Yellow Fever

Yellow fever is a hemorrhagic fever caused by the yellow fever virus, a positive-sense RNA virus belonging to the genus *Flavivirus*, the same genus of the dengue fever virus (Lindenbach and Rice, 1994). The virus is an arbovirus, transmitted from person to person by *Aedes aegypti*, a domesticated species of mosquito. *A. aegypti* requires temperatures of at least 72°C, making it well suited for the tropical cities of South America and Africa. More than just an ideal climate, the cities also provide a multitude of hosts. *A. aegypti* becomes a carrier for the virus after feeding on an infected person, but it does not become infective until the virus has incubated in the new host for 10-12 days (Gubler, 2004). After this incubation period, the mosquito remains infective for life and can even pass the virus to its larvae, which commonly lay waiting in the community drinking water and other moist locations. Although *A. aegypti* is the most common vector, the yellow fever virus has been found in a multitude of other species that not only appear near cities but also in the jungle regions, where the virus is maintained in lower primates (Garrett, 1994).

Yellow fever symptoms begin after a 3-6 day incubation period and often proceed in two phases: acute and toxic. The acute phase is characterized by fever, muscle pain, headaches, shivers, loss of appetite, nausea or vomiting. Because these symptoms are indicative of several other common ailments, such as the flu and malaria, yellow fever is often misdiagnosed or undiagnosed altogether. Acute symptoms usually improve within 3-4 days, but for 15% of infected patients they worsen. After a 24 hour period of remission, these patients enter the toxic phase. The toxic phase, as its name suggests, involves more severe, unique symptoms: high fever, jaundice (hence *yellow* fever), internal bleeding, black vomit (the color of which is caused

by dead blood cells), kidney failure, and coma. Within 14 days of entering the toxic phase, approximately half of those infected with yellow fever die (Dennis, 1969).

The first recorded epidemic of yellow fever occurred in 1648 in Yucatan, Cuba, but this was likely part of a larger outbreak that ravaged the Caribbean islands from 1647-1649. Despite the semi-recent emergence, the virus probably evolved in Africa about 3000 years ago. When Europeans began colonizing and engaging in slave trade, the virus was transported to the New World from the mosquitoes and larvae hiding among the cargo. In the Americas it had a deadly effect. With its remarkably virulent nature and no immunity in the population, yellow fever would prove to be a recurring problem that continues today. In 1690, the virus found its way into North America, infecting major port cities such as Charleston, New York, and Philadelphia. In 1793 one particularly deadly outbreak occurred that caused most of Philadelphia's inhabitants, including members of the federal government, to flee the city. Of Philadelphia's 60,000 residents, 5,000 succumbed to the disease that year. The origin of the disease was mistakenly blamed on the miasma of rotting coffee and garbage that littered the city and the wharf. By 1820 the outbreaks were confined to the South, where they occurred almost every summer. Yellow fever became an accepted part of life in the South for the next 80 years until the virus was finally eradicated from the US in 1905 through management of the mosquito population (Sherman, 2007).

Despite the prevalence of outbreaks throughout the 18th and 19th centuries, no one knew how the virus was spread. It was commonly believed that transmission occurred through patients' contact with black vomit or the miasma from rotting garbage. In 1802 a medical student at the University of Pennsylvania, Stubbins Firth, performed a series of self-experiments, extensively exposing himself to black vomit and other items contaminated by a yellow fever

patient. Though he even went as far as ingesting black vomit and smearing it into a wound, he never contracted the disease. Unfortunately, of course, his experiments failed to reveal how yellow fever spread, revealing instead only how it *didn't* spread (Sherman, 2007).

In 1900 a group of physicians and scientists dubbed the Yellow Fever Commission went to Cuba in hopes of determining the identity of the pathogen and its method of transmission. Carlos Finlay, a Cuban scientist, had theorized that the disease was spread by blood suckers (*A. aegypti*), but his experiments yielded no data to support the claim, largely because he had not allowed enough time between the initial mosquito bite and the transmission (Sherman, 2007). The Commission began further experimenting with Finlay's hypothesis using human trials. In their first experiment, subjects were bitten by a female mosquito immediately following its feeding on an infected patient. None of the subjects contracted the disease. However, a most curious incident occurred twelve days later when a member of the Commission was bitten by one of the mosquitoes used in the first trial and became very ill. Unsure of the significance of the incident, two other members of the Commission volunteered to be bitten by the mosquitoes. Both contracted yellow fever and, tragically, one perished as a result. With only three instances of transmission, the Commission declared that mosquitoes were the disease's vector and that an incubation period was required for the host mosquito to become infective. The conclusion was met with skepticism, many people still convinced of the long established theory that black vomit was the vehicle through which yellow fever spread (Sherman, 2007) The Commission returned to Cuba intent on proving their hypothesis through further experimentation. They placed seven volunteers in a house with screened windows (to prevent insects from entering), and exposed them to the black vomit, stool, and clothes of infected patients. Not one of the seven volunteers contracted the disease. In their next experiment they partitioned a house with mesh, placing 15

infected mosquitoes on one side and none on the other. Only the people that resided with mosquitoes contracted the disease, concretely identifying *A. aegypti* as the transmission vector (Sherman, 2007).

Following this, the Commission determined that the pathogen was a virus, having eliminated the possibility of it being a bacterium due to its lack of presence in the blood. Further backing this claim, when they injected filtered infected blood into a subject, which would filter out larger organisms such as fungi and bacteria, the subject developed the disease.. This discovery began a race to develop a vaccine. Vaccine development received a great boost with the discovery that both Rhesus monkeys and mice could be infected with the virus. The animals provided a living test subject for the vaccine that was not a human. (Sherman, 2007).

Now, cultures are grown in a variety of tissues including mouse embryo intestinal, porcine kidney, and mosquito (Converse, 1971). Max Theiler, a Harvard scientist, discovered that, by serially passing the virus through hosts, it became less virulent to the animals and eventually became stable. Mice, he found, were protected from a lethal dose of virus if they were first exposed to blood serum of an immune subject, but this method was too costly and material inefficient to be implemented for global use. He continued to develop his serially passed virus as a vaccine. In 1937, one of his strains, dubbed 17D, mutated and lost its virulence, but still produced antibodies effective against the lethal strain. Effective and inexpensive, Theiler had created the ideal vaccine (Sherman, 2007).

Despite the development of a vaccine, yellow fever remains endemic in a number of areas in South America and Africa and despite a sweeping effort to eliminate *A. aegypti* populations in cities in the 1970's, focusing on vaccination programs and eradication of the domestic mosquito population. One reason for its continued presence stems from the diversity in

vector species. In reality, there are two concurrent cycles of disease: the urban cycle in the city and the sylvan cycle in the jungle. Wild mosquito species and lower primates provide a natural reservoir for the virus, making it impossible to eradicate in sylvan environments. With the increase of travel and eco-tourism, people are exposing themselves more to the sylvan cycle, providing an opportune moment for the virus to reemerge in the urban cycle. The ease of travel is spreading the potential reach of the disease worldwide, and the recovery and spread of *A. aegypti* populations bring the virus ever closer to an epidemic (Gubler, 2004).

References:

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