Yellow Fever 17D: Miracle at 66th Street

Scott B Halstead, MD
Uniformed Services University of the Health Sciences
Bethesda, MD
Miracle: The Final Step

Hugh Smith giving YF 17D, Brazil, 1937
How did that miracle happen?
The story of yellow fever – part 1

• Pre-1900. Finlay’s theory of transmission.
• 1900 Walter Reed. *Aedes aegypti* a vector; YF a virus.
• 1901 Gorgas invents *Aedes aegypti* control. YF disappears from Havana
• 1902 Gorgas: “I look forward in the future to a time when yellow fever will have entirely disappeared as a disease to which mankind is subject”
• 1903 Oswaldo Cruz begins control program. Rio de Janeiro.
• 1904 Gorgas begins control of malaria, YF in Panama.
Early heroes
The story of yellow fever – part 2

• 1913 The Rockefeller Foundation chartered.
• 1914 Wickliffe Rose, Director International Health Commission, travels to Far East. Learns of fears of importing yellow fever through the Panama Canal.
• 1915 Gorgas agrees to work with the RF on controlling urban YF.
The RF Yellow Fever Commission

Mr. Wickliffe Rose
Director, International Health Board, 1916-23
The story of yellow fever – part 3

- 1918 The RF Yellow Fever Commission selects Guayaquil.
- 1919-27 Campaigns in key centers: Ecuador, Peru, Colombia, Mexico, Brazil Central America. Urban YF gone.
- 1925 West Africa YF Commission sets up lab in Lagos. Isolates Asibi strain.
- 1928 Noguchi dies. American and African YF shown to be identical viruses.
The RF in America and Africa
The story of yellow fever – part 4

• 1928 Transmission of YF by mosquitoes other than *Ae aegypti*.
• 1930 Search for YF cases in smaller towns in the Americas.
The story of yellow fever – part 5

- 1931  Serological surveys in America and Africa show widespread YF immunity.
- 1931  Invention of the viscerotome.
- 1932  First Zero premises index.
- 1933  Soper proves jungle yellow fever.
Jungle yellow fever
Jungle yellow fever – need for a vaccine

"...Jungle yellow fever may be the more natural form of yellow fever endemicity and...urban aegypti-transmitted yellow fever...an exotic form maintained with more difficulty than...the jungle type"

Fred L. Soper
The story of yellow fever vaccine part 1

- 1928  RF opens New York laboratory.
- 1930  Theiler discovers white mouse, used for virus recovery and antibody tests.
- 1930  Sawyer develops first YF vaccine: Mouse brain virus plus immune serum.
- 1934  French neurotropic YF vaccine.
The laboratories of the Rockefeller Institute at 66th Street - 1928
66th Street entrance to Rockefeller University
1920’s virus lab
Decision makers/actors

Frederick Russell
Director, International Health Division, RF
1927 -35

Wilbur Sawyer
Director, International Health Division, RF
1935 - 1944
The story of yellow fever vaccine
part 2

- 1934-6 Cultivation of YFV in tissue culture. (Lloyd, Theiler, Ricci, TRSTMH 1936)
- 18 passages in cultured embryonic mouse tissue.
- 58 passages in minced chick embryo.
- 160 + passages in chick embryo minus spinal cord and brain.
- In vitro passage 114 lost viscerotropism for monkeys and neurotropism for mice and monkeys. (Theiler, Smith JEM 1937a)
- Only 1 of 6 passage lines in chick embryo without neural tissue showed 17D mutation.
New heroes

Max Theiler  
Nobel Laureate  
1951

Hugh Smith
The story of yellow fever vaccine part 3

- 1936 Rare, stable mutant proved. Immunized monkeys protected (Theiler, Smith, JEM 1937a). Immunize humans. Safe, 100% antibody (Theiler, Smith, JEM 1937b).
- Theiler unable to again obtain 17D mutant on repeating chick explant culture passaging.
The story of yellow fever vaccine part 4

- Jan 1937. Smith brings 17D to Brazil
- Mar 1937 Smith produces 40,000 doses of vaccine, passages 205-287, in 7 day-old chick embryos. Vaccine efficacious, safe.
- Sep 1937 600,000 doses of 17 D locally produced.
YF 17 /D for delivery
Fig. 69. Yellow fever vaccination equipment from a field kit. This kit is equipped with cultured 17D virus (1937).
Mass vaccination
Adjusting YF 17D

• 1938: Field trials show increased incidence of encephalitis in children at different passage levels of YF 17D.
• Some passage levels of vaccine are over-attenuated.
• 1941: Seed lot system introduced by Rio de Janeiro laboratory.
Things we still do not know about yellow fever
How does YF 17 D work?
YF 17 D immune protection

- Long attributed to antibodies.
- Newly discovered importance of T cell immunity.
Questions:
1) Why did urban YF go to America and not Asia?
2) Why has American jungle YF not re-urbanized?
“Out of Africa”
yellow fever’s home

Yellow fever 1500s? Never Why?
Yellow fever
“Out of Africa”

- Three African genotypes:
  - West Africa, Angola, Central Africa
- Only the West African genotype can be transmitted by urban *Aedes aegypti aegypti* and has produced many urban outbreaks in Africa.
- During 1500 - 1600, the West African genotype emerged into an American urban cycle.
- This virus entered a complex American sylvatic cycle.
Why did pandemic YF never cross the Indian ocean?
Transmission blockage

• Is it possible that Central African YF genotypes adopted to be transmitted by *Aedes africanus* cannot be transmitted by *Aedes aegypti aegypti*?

• Central African YF “blocks” West African YF virus from reaching East Coast.

• No YF virus on East Coast, no YF virus available for transport across the Indian Ocean.
“Out of Africa”
yellow fever’s home

Yellow fever 1500s?  Never Why?
Why has American sylvatic YF not urbanized?
Yellow fever zoonotic cycle
Questions about yellow fever behavior

- American jungle yellow fever has not been successfully introduced into the urban cycle in South American towns and cities.
- Is it possible that American jungle yellow fever virus is so poorly adapted to *Aedes aegypti* that it cannot be easily urbanized?
"...Jungle yellow fever may be the more natural form of yellow fever endemnicity and...urban aegypti-transmitted yellow fever...an exotic form maintained with more difficulty than...the jungle type"

Fred L. Soper
Happy 80th anniversary of 17D!!
Thank you