# *Searching for Yellow Fever*: The Rockefeller Foundation, Haddow Towers, Monkeys, and the Discovery of the Zika Virus

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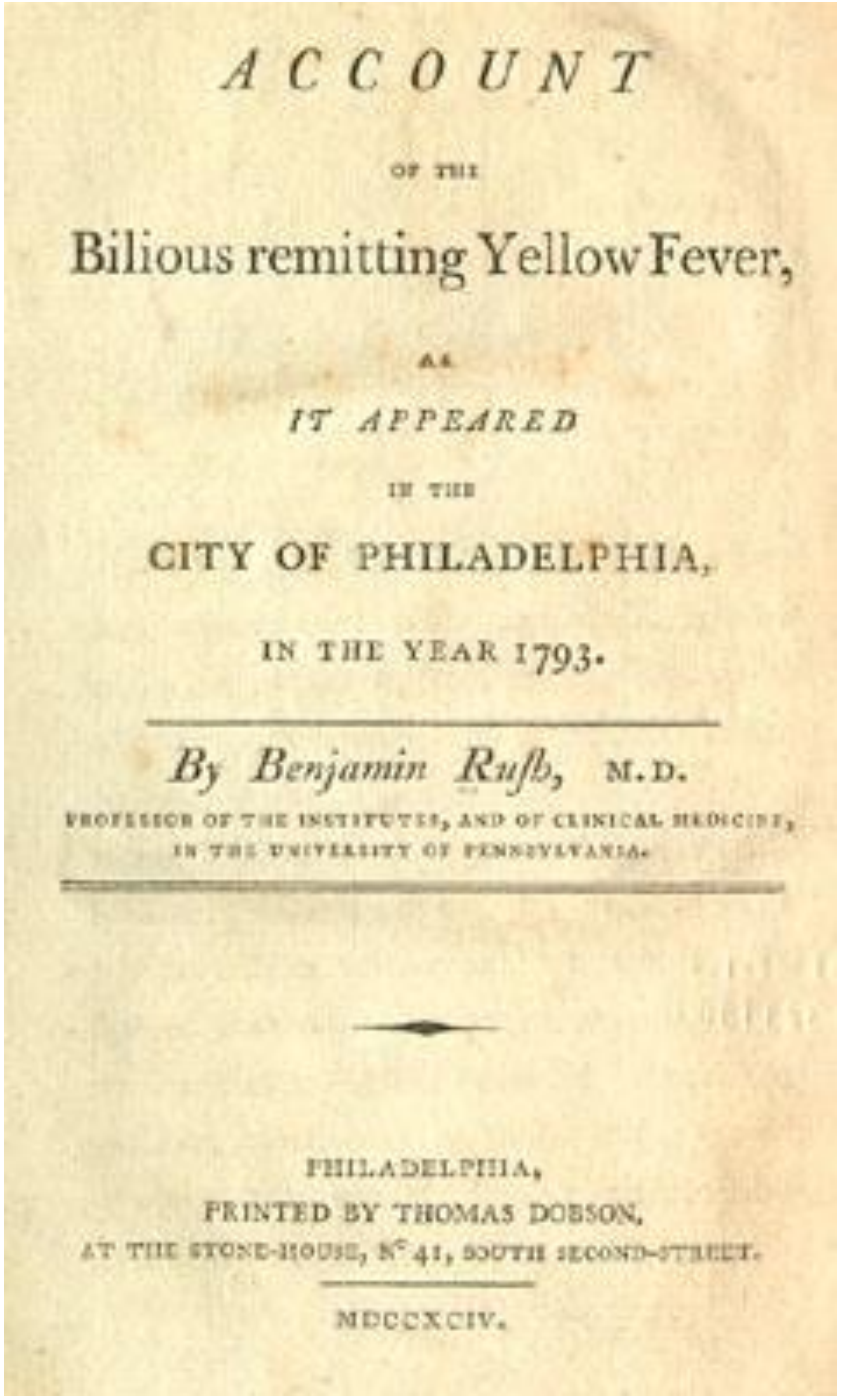

ACCOUNT

OF THE

Bilious remitting Yellow Fever,

AS

IT APPEARED

IN THE

CITY OF PHILADELPHIA,

IN THE YEAR 1793.

By Benjamin Rush, M.D.

PROFESSOR OF THE INSTITUTES, AND OF CLINICAL MEDICINE, IN THE UNIVERSITY OF PENNSYLVANIA.

PHILADELPHIA,
PRINTED BY THOMAS DOBSON,
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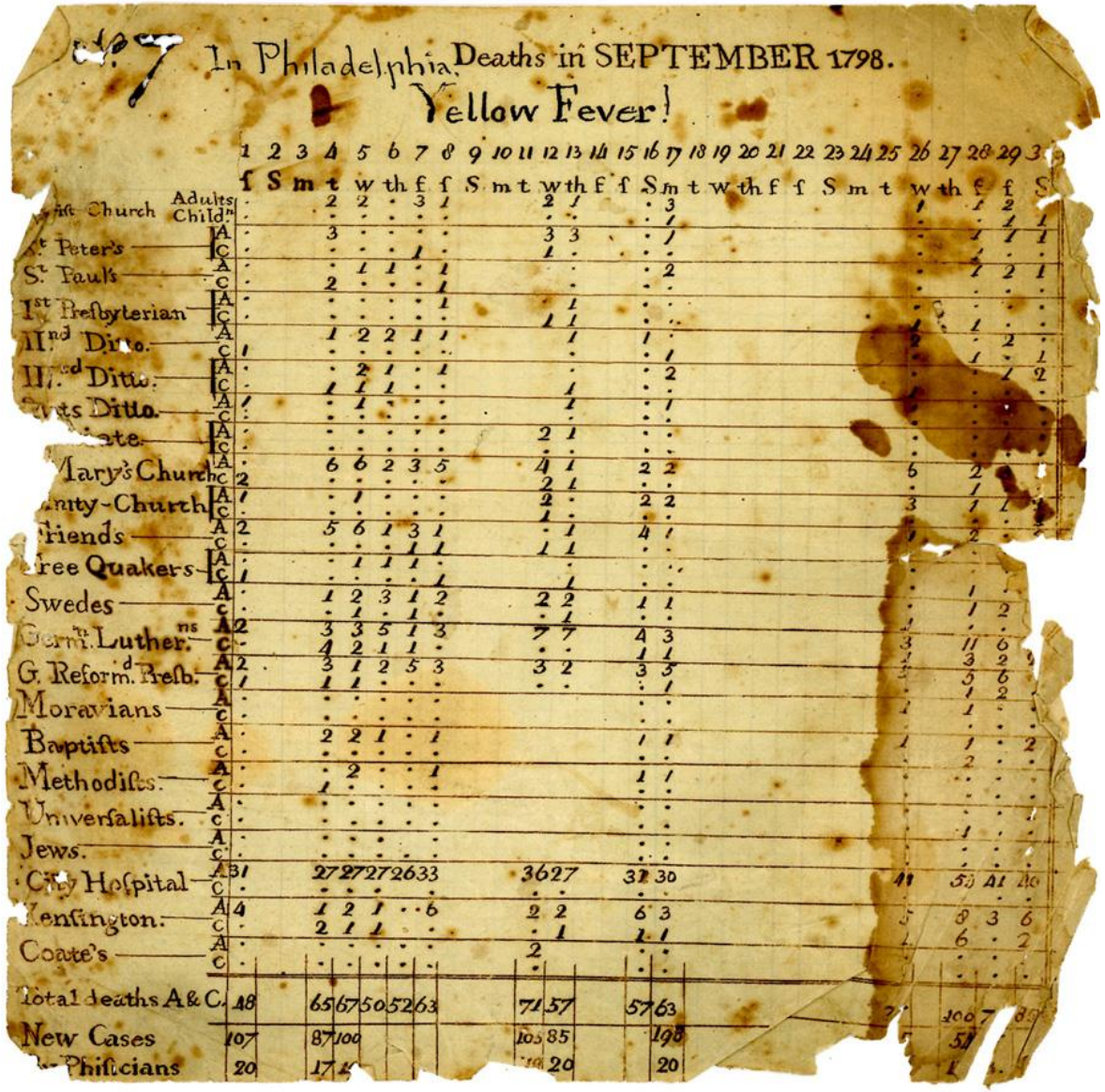
MDCCXCIV.

# Yellow Fever – A Global Scourge

- Yellow fever originated in Africa, and spread to the Western Hemisphere in the mid-17$^{th}$ century
- At least 25 major outbreaks occurred in North America
- The Philadelphia yellow fever outbreak of 1793 resulted in  the death of 9% of the population, prompting George Washington, Benjamin Franklin and other dignitaries to flee the city, and transfer the seat of the new government of the United States
- There was no treatment for the disease, and it was not known how it was spread or acquired

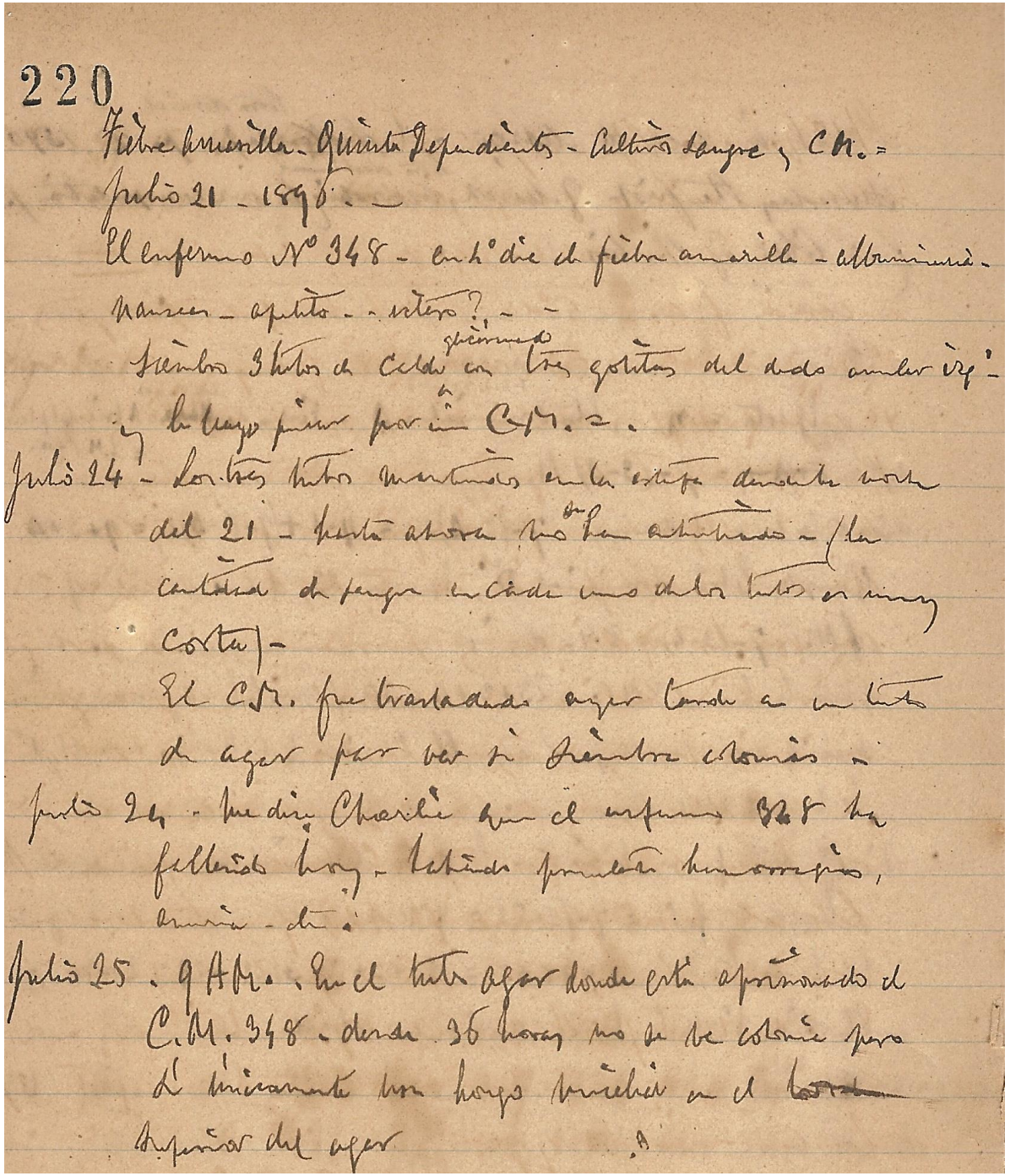
# Yellow Fever – A Global Scourge




- Additional major outbreaks occurred in Philadelphia in 1798, Haiti in 1790, Savannah in 1820, New Orleans in 1853, Norfolk in 1855, Texas in 1867, the Lower Mississippi Valley in 1878, and during the construction of the Panama Canal from 1882 to 1889
- The advent of the Spanish American War in 1898 prompted the United States to form a commission to investigate yellow fever in Cuba
- Of the approximately 3,000 American soldiers who died in Cuba during the war, 2,000 died from yellow fever

# Yellow Fever – Discovery of Mosquito Transmission

- Carlos Finlay MD was a Cuban physician who first hypothesized (in 1881) that yellow fever was transmitted by mosquitoes
- When Major (Dr.) Walter Reed was sent to Cuba by the Surgeon General to investigate the cause of yellow fever he adopted, and later prove,d Finlay's mosquito transmission hypothesis


220
Fiebre amarilla - Quinta Dependientes - Cultivo sangre y C.M. =
Julio 21 - 1900. —
El enfermo Nº 348 - en 4º dia de fiebre amarilla - albuminuria -
nausea - apatito - - ictero ? - -
Siembra 3 tubos de Celdo con tres gotitas del dedo anular izq.
y la tapa pinta por un C.M. =.
Julio 24 - Los tres tubos mantenidos en la estufa desde ayer
del 21 - hasta ahora no han aturbiado - (la
cantidad de sangre en cada uno de los tubos es muy
corta) -
El C.M. fue trasladado ayer tarde a un tubo
de agar por ver si siembra colonias -
Julio 24 - Me dice Charlie que el enfermo 348 ha
fallecido hoy - Estando presente hemorragias,
anuria - etc -
Julio 25 . 9 A.M. - En el tubo agar donde está sembrado el
C.M. 348 - desde 36 horas no se ve colonia pero
si ligeramente un poco turbio en el
depósito del agar

# Yellow Fever – Discovery of Mosquito Transmission

- Yellow fever was the first microbial agent shown to be transmitted by a mosquito – by Dr. Carlos Finlay
- General Leonard Wood, a medical doctor and the U.S. military governor of Cuba in 1900, said "*The confirmation of Dr. Finlay's doctrine is the greatest step forward made in medical science since Jenner's discovery of the vaccination* [for smallpox]."

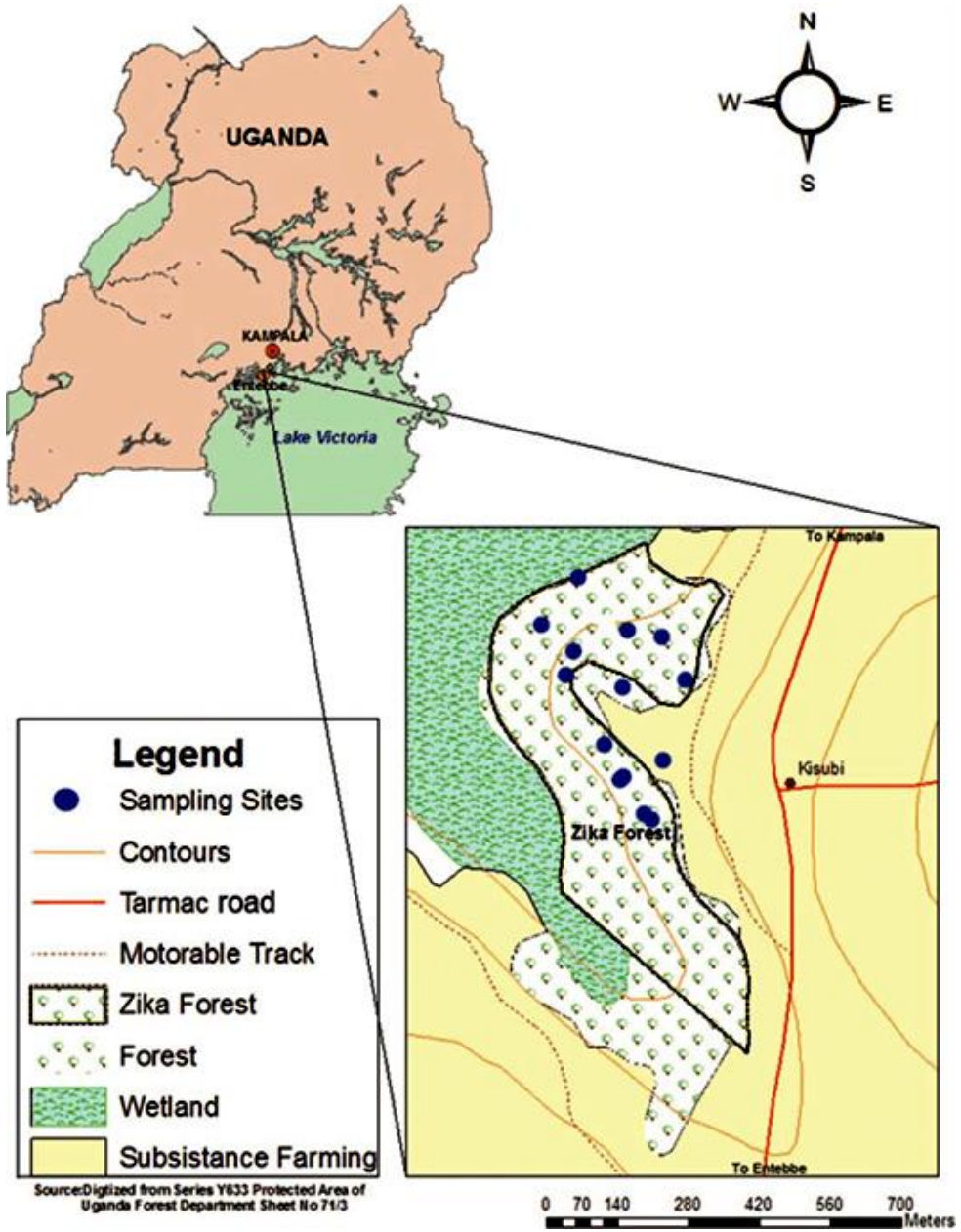
# The Rockefeller Foundation Yellow Fever Commission

- In 1913, the American businessman and philanthropist John D. Rockefeller established a foundation "*to promote the well-being of mankind throughout the world*."
- Following efforts to control hookworm disease, the Foundation turned their attention to the global yellow fever ("*yellow jack*") situation
- Laboratories were established in multiple locations in Latin America and in Africa to study the disease

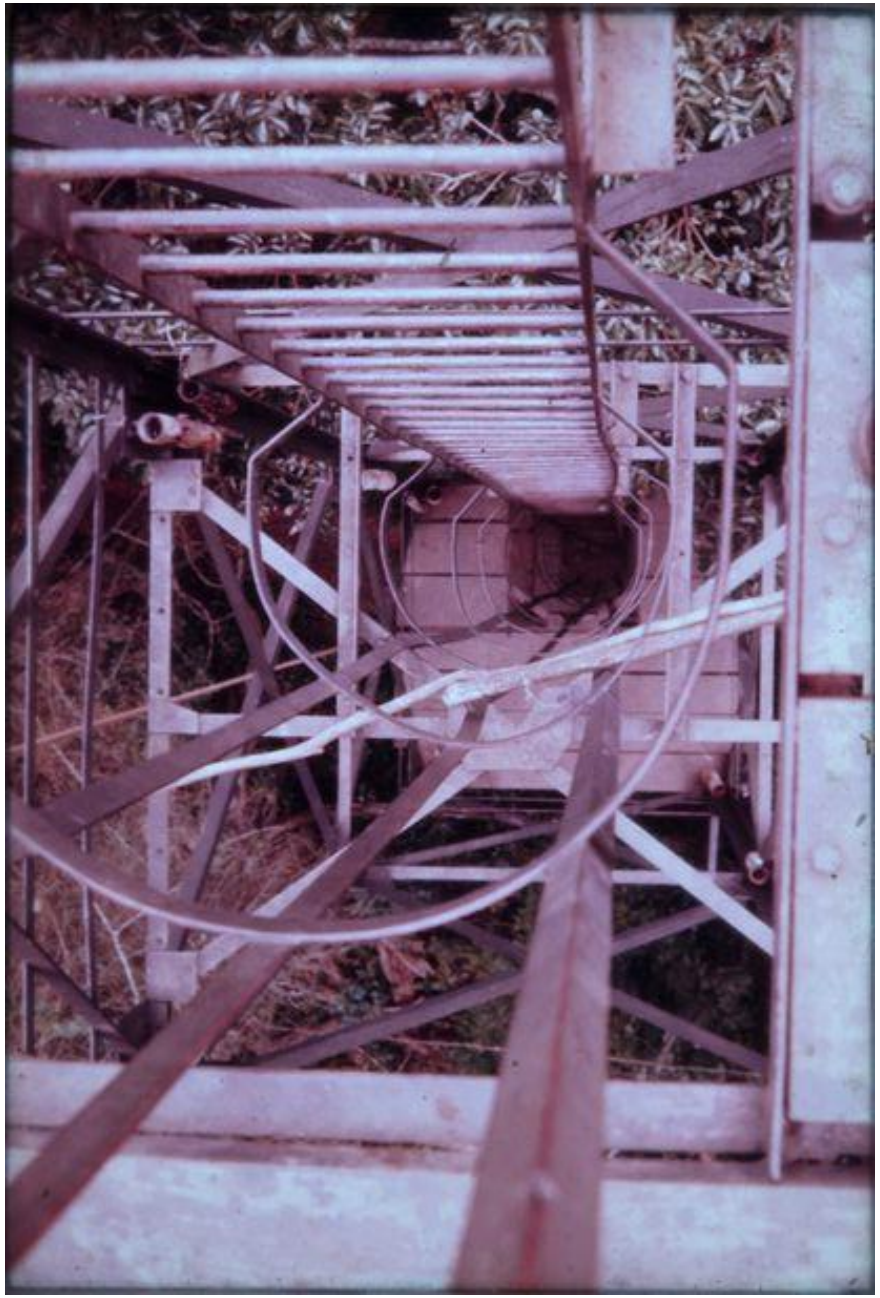
# Rockefeller Comes to the Zika Forest In Uganda

- In a little-known area 25 km outside of Kampala, the Zika (Ziika) Forest, a team of Rockefeller investigators established a field laboratory to study yellow fever in Uganda just after World War II.
- The team included George W.A. Dick, Alexander J. Haddow, and Stuart F. Kitchen
- The Zika Forest was an ideal location to study the natural history and mosquito vectors of this disease

# LOCATION OF THE ZIKA FOREST IN UGANDA

# Construction of the Haddow Towers



- Alexander Haddow, the team entomologist, constructed 120-foot tall steel towers (known as Haddow towers) where mosquitos, birds, bats and a variety of animals could be captured and studied to the presence of yellow fever

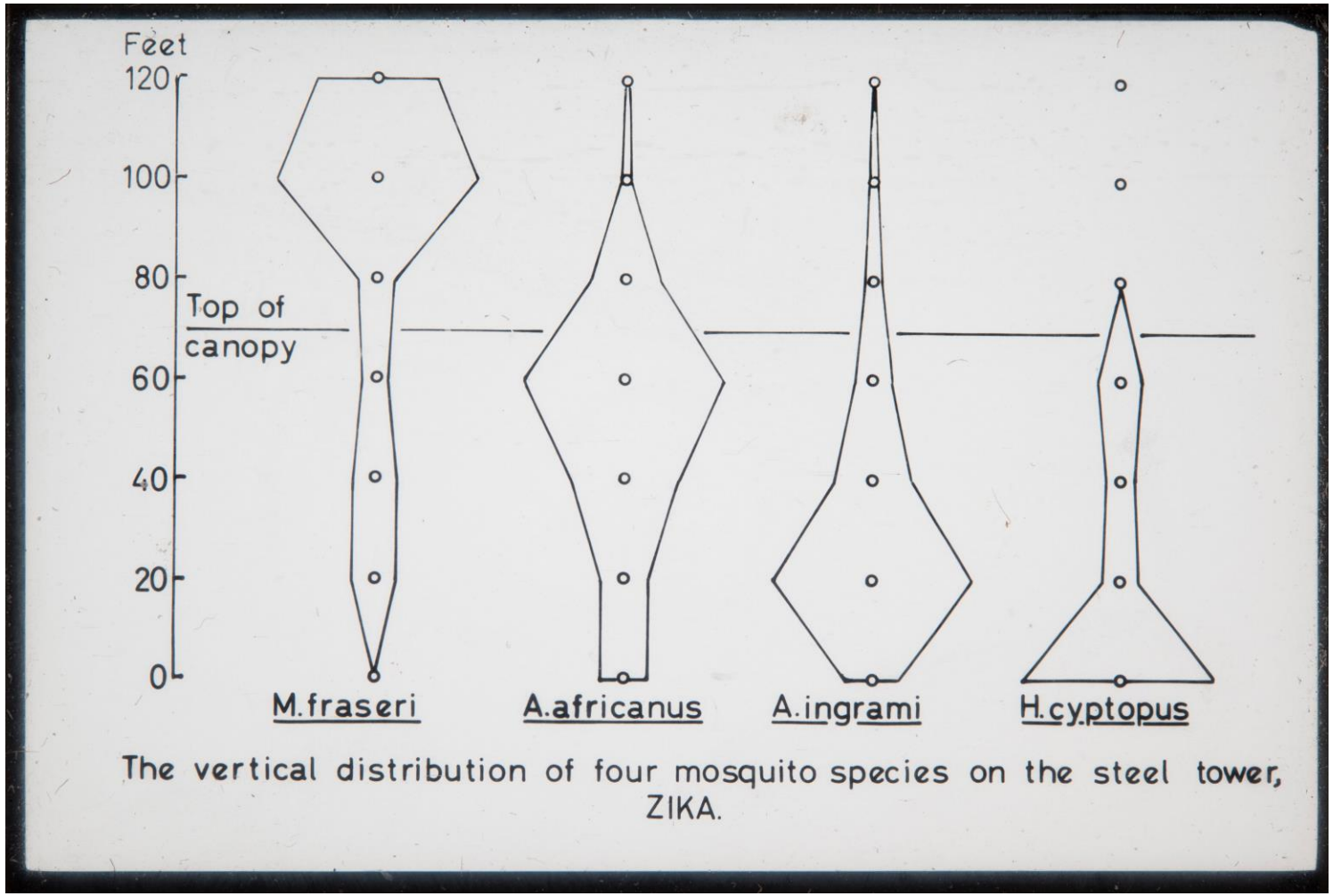
# The Haddow Towers – 120 Feet Tall

Alexander Haddow having a discussion with colleagues under the steel tower used for mosquito and animal research, circa 1947

# Sentinel Monkeys were Used to Identify Arboviruses

- Captive monkeys and collection cages were placed in cages suspended in trees at different heights above the ground, because feeding preferences of certain mosquitos vary by height
- These caged “sentinel” monkeys had their blood tested at intervals to look for the presence of yellow fever and other arboviruses
- Local boys were hired to catch the mosquitos, as seen by this boy climbing to reach an 82-foot platform

# Mosquito Distributions by Height from Ground Level




The vertical distribution of four mosquito species on the steel tower, ZIKA.

- An original diagram illustrating the entomological results from a Haddow Tower
- The graphs give the vertical distribution of four mosquito species, including *Aedes africanus*, the species from which the Zika virus was initially isolated
- It can be seen that *A. africanus* is most active at 60 feet (18 meters), just beneath the top of the forest canopy

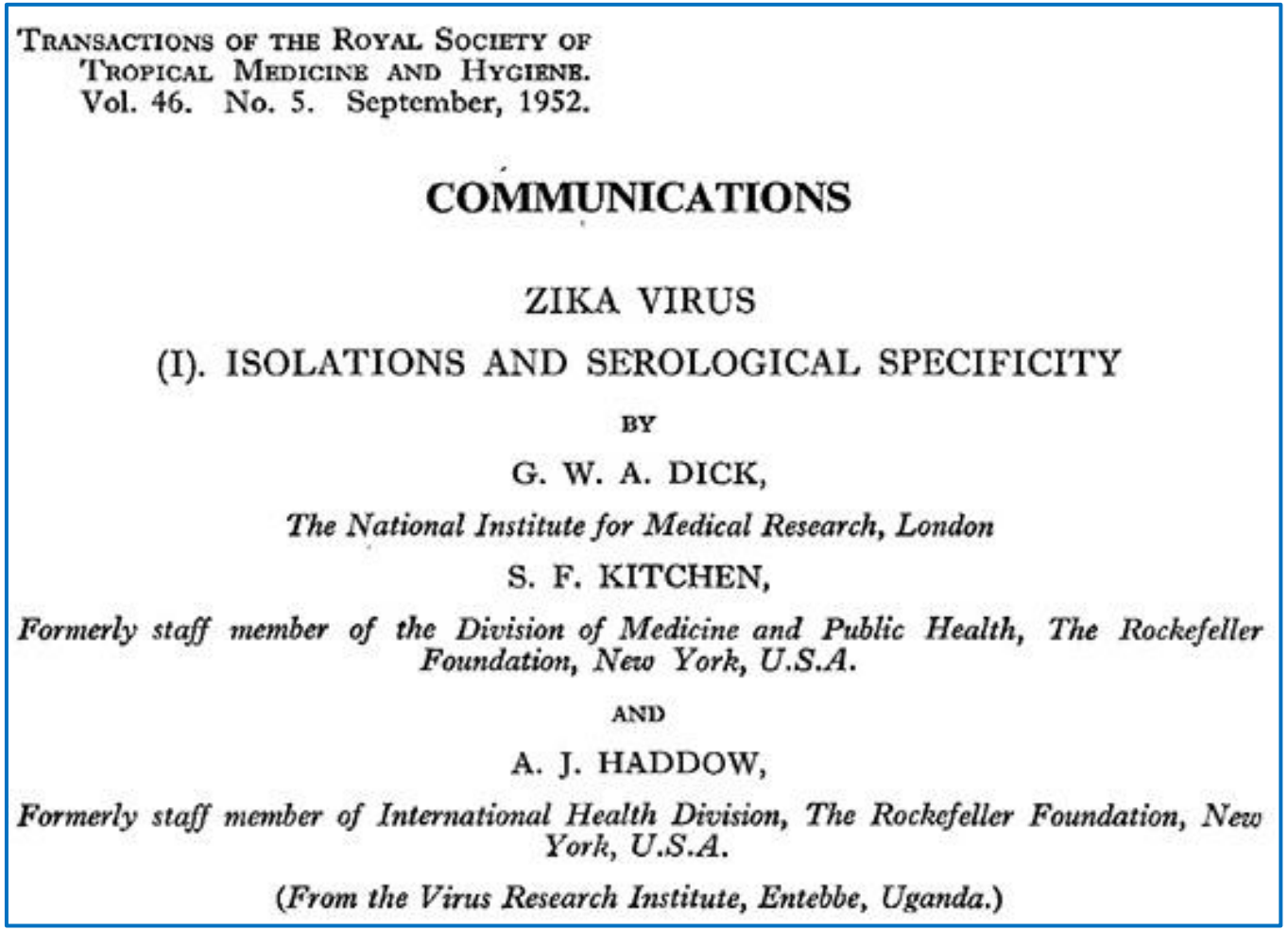
# Discovery of the Zika Virus in 1947

- On April 18, 1947, one of the rhesus macaques, named *Rhesus 766*, developed a fever of 39.7 degrees, about 2 degrees higher than normal
- The monkey was set to the Entebbe laboratory, where its blood was taken and inoculated via intracerebral and intraperitoneal routes into Swiss albino mice and a uninfected macaque names *Rhesus 771*
- *Rhesus 771* and the intraperitoneally-inoculated mice failed to develop infection
- The mice inoculated intracerebrally became ill starting 10 days after injection

# Identification of the Zika Virus

- A small virus, then termed a “filterable agent”, was recovered from the brain of infected mice
- The same virus was isolated from the blood of *Rhesus 766*, who had developed fever but no illness
- The following year, on January 11$^{th}$ & 12$^{th}$, 1948, scientists were trapping mosquitos on a Haddow tower
- After homogenizing 86 *A. africanus* mosquitos, the mixture was mixed with blood-saline solution and injected into mice and a macaque

# Identification & Publication of the Zika Virus



TRANSACTIONS OF THE ROYAL SOCIETY OF
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## COMMUNICATIONS

### ZIKA VIRUS

### (I). ISOLATIONS AND SEROLOGICAL SPECIFICITY

BY

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*The National Institute for Medical Research, London*

S. F. KITCHEN,

*Formerly staff member of the Division of Medicine and Public Health, The Rockefeller Foundation, New York, U.S.A.*

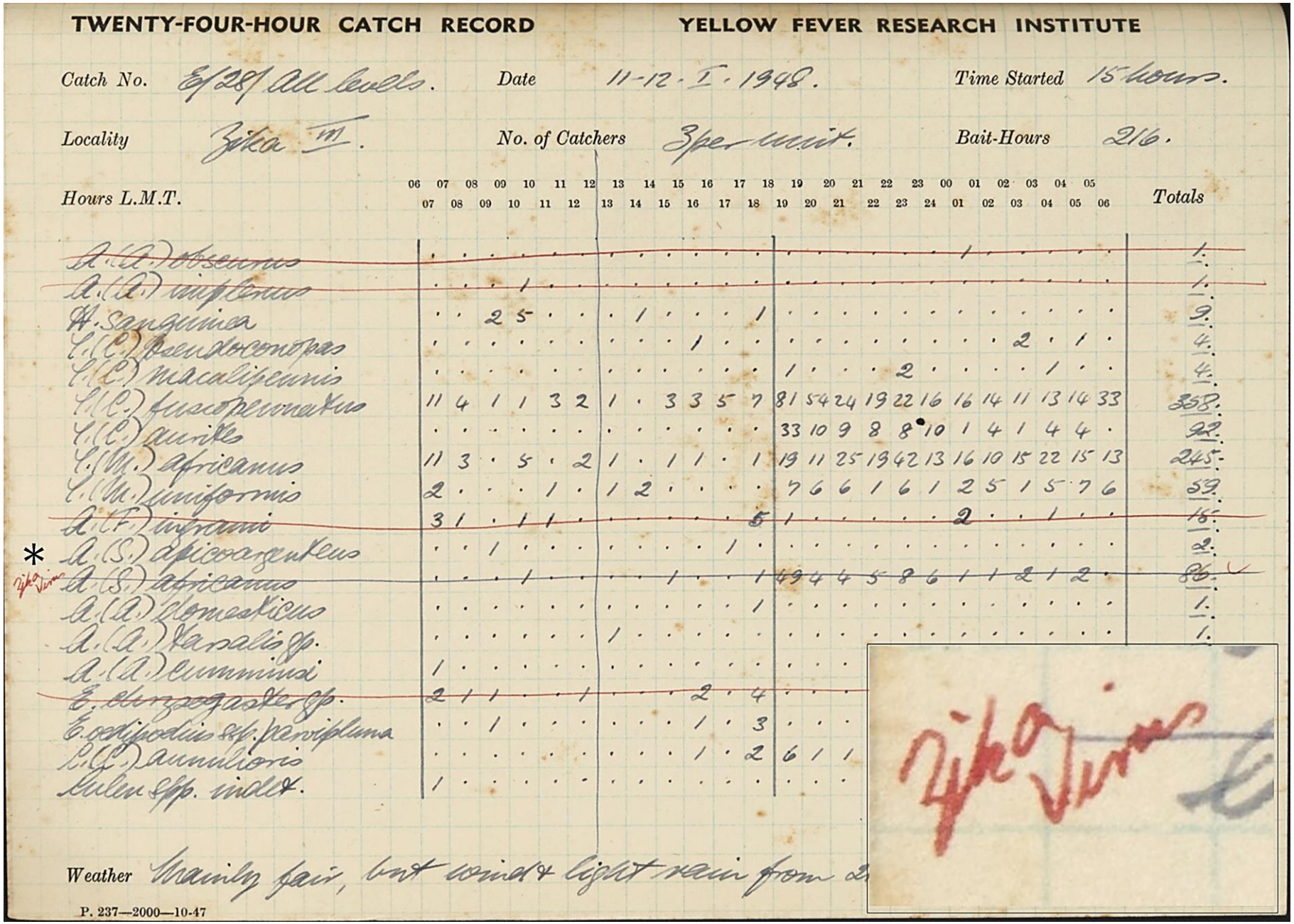
AND

A. J. HADDOW,

*Formerly staff member of International Health Division, The Rockefeller Foundation, New York, U.S.A.*

(*From the Virus Research Institute, Entebbe, Uganda.*)

- 7 days after their brains were injected with the mixture, the mice "appeared inactive" – testing revealed the same filterable agent as had been isolated from *Rhesus 766*
- The newly-inoculated macaque, *Rhesus 758*, never became ill
- When its serum was inoculated intracerebrally into uninfected mice, they became ill and died
- The Rockefeller team named the new agent "Zika Virus", and published their data several years later in 1952



TWENTY-FOUR-HOUR CATCH RECORD — YELLOW FEVER RESEARCH INSTITUTE

Catch No. E/28/ all levels. Date 11-12-I-1948. Time Started 15 hours.

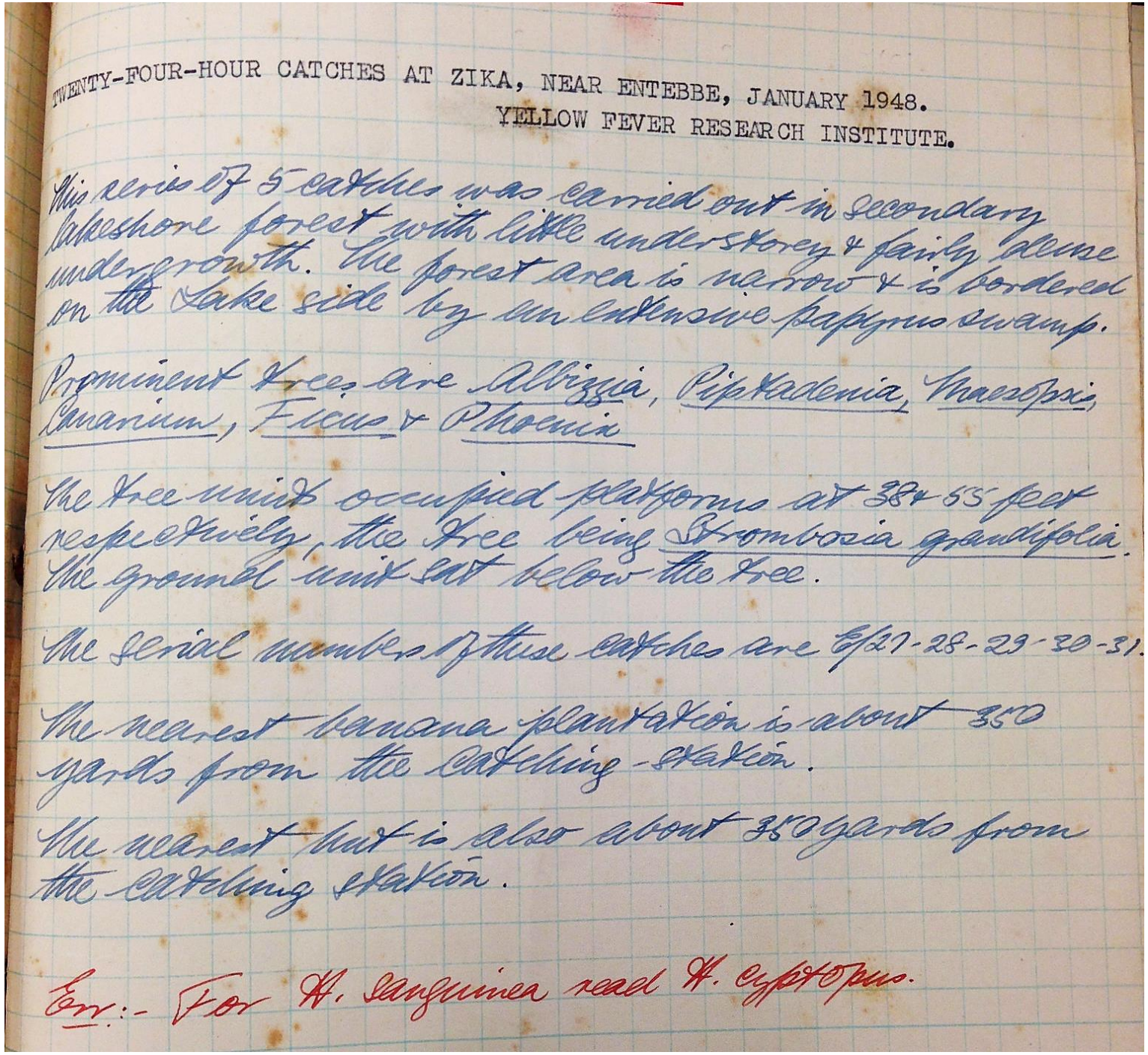
Locality Zika III. No. of Catchers 3 per unit. Bait-Hours 216.

| Hours L.M.T. | 06 07 | 07 08 | 08 09 | 09 10 | 10 11 | 11 12 | 12 13 | 13 14 | 14 15 | 15 16 | 16 17 | 17 18 | 18 19 | 19 20 | 20 21 | 21 22 | 22 23 | 23 24 | 00 01 | 01 02 | 02 03 | 03 04 | 04 05 | 05 06 | Totals |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A. (A.) obscurus | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . | 1 |
| A. (A.) implexus | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 |
| H. sanguinea | . | . | 2 | 5 | . | . | . | 1 | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | 9 |
| L. (C.) pseudoconopas | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | 2 | . | 1 | . | 4 |
| L. (C.) macalisteri | . | . | . | . | . | . | . | . | . | . | . | . | 1 | . | . | . | 2 | . | . | . | . | 1 | . | . | 4 |
| L. (C.) fuscopennatus | 11 | 4 | 1 | 1 | 3 | 2 | 1 | . | 3 | 3 | 5 | 7 | 81 | 54 | 24 | 19 | 22 | 16 | 16 | 14 | 11 | 13 | 14 | 33 | 358 |
| L. (C.) aurites | . | . | . | . | . | . | . | . | . | . | . | . | 33 | 10 | 9 | 8 | 8 | 10 | 1 | 4 | 1 | 4 | 4 | . | 92 |
| L. (M.) africanus | 11 | 3 | . | 5 | . | 2 | 1 | . | 1 | 1 | . | 1 | 19 | 11 | 25 | 19 | 42 | 13 | 16 | 10 | 15 | 22 | 15 | 13 | 245 |
| L. (M.) uniformis | 2 | . | . | . | 1 | . | 1 | 2 | . | . | . | . | 7 | 6 | 6 | 1 | 6 | 1 | 2 | 5 | 1 | 5 | 7 | 6 | 59 |
| A. (F.) infirmus | 3 | 1 | . | 1 | 1 | . | . | . | . | . | . | 5 | 1 | . | . | . | . | . | 2 | . | . | 1 | . | . | 16 |
| * A. (S.) apicoargenteus | . | . | 1 | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | 2 |
| Zika Virus A. (S.) africanus | . | . | . | 1 | . | . | . | . | 1 | . | . | 1 | 49 | 4 | 4 | 5 | 8 | 6 | 1 | 1 | 2 | 1 | 2 | . | 86 |
| A. (A.) domesticus | . | . | . | . | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | 1 |
| A. (A.) karwalis ssp. | . | . | . | . | . | . | . | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 |
| A. (A.) cummingsi | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 |
| E. theobaldi ssp. | 2 | 1 | 1 | . | . | 1 | . | . | . | 2 | . | 4 | . | . | . | . | . | . | . | . | . | . | . | . | 10 |
| E. ocellatus ssp. peryassui | . | . | 1 | . | . | . | . | . | . | 1 | . | 3 | . | . | . | . | . | . | . | . | . | . | . | . | 5 |
| P. (P.) aurulionis | . | . | . | . | . | . | . | . | . | 1 | . | 2 | 6 | 1 | 1 | . | . | . | . | . | . | . | . | . | 10 |
| Aulacomyia ssp. indet. | 1 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | 1 |

Weather Mainly fair, but wind & light rain from 2

P. 237—2000—10-47

A page from Dr. Haddow's notes showing the standard format he used to record the results for 24-hour catches of mosquitoes. This was a technique he pioneered, where all the biting insects at a specific location would be caught, stored, and grouped by the hour in which they were caught. The mosquitoes would later be identified, and the number of each species caught each hour at each level was recorded. In this particular record, the entry for A. (S) africanus is annotated “Zika Virus” in red ink (left side of image [asterisk] and inset): this was the first batch of mosquitoes from which the Zika virus was isolated.



TWENTY-FOUR-HOUR CATCHES AT ZIKA, NEAR ENTEBBE, JANUARY 1948.
YELLOW FEVER RESEARCH INSTITUTE.

This series of 5 catches was carried out in secondary lakeshore forest with little understorey & fairly dense undergrowth. The forest area is narrow & is bordered on the lake side by an extensive papyrus swamp.

Prominent trees are Albizzia, Piptadenia, Maesopsis, Canarium, Ficus & Phoenix

The tree units occupied platforms at 38 & 55 feet respectively, the tree being Strombosia grandifolia. The ground unit sat below the tree.

The serial numbers of these catches are E/27-28-29-30-31.

The nearest banana plantation is about 350 yards from the catching-station.

The nearest hut is also about 350 yards from the catching station.

Err:- For H. sanguinea read H. cyprotopus.

**This page describes "Zika III", the location in the Zika forest where the mosquitoes that gave the first isolation of the Zika virus were caught in 1948.**

**"This series of 5 catches was carried out in secondary lakeshore forest with little understorey + fairly dense undergrowth. the forest area is narrow + is bordered on the lake side by an extensive papyrus swamp.**

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**The serial numbers of these catches are E/27-28-29-30-31. The nearest banana plantation is about 350 yards from the catching-station.**

**The nearest hut is also about 350 yards from the catching station.**

# A New Virus, *But Where Was the Disease*?

- Following its identification as a newly-discovered arbovirus in 1948, no human disease was identified with the Zika virus
- The first evidence for human infection occurred 4 years later.

- In 1952, results of a serological survey in Uganda showed that 6.1% of 99 sera tested had neutralizing antibodies to the Zika virus
- In a 1954 investigation of a suspected fever case, Zika virus was suspected; but a closely-related flavivirus, Spondweni virus, was later shown to be the infective agent

# *Eventually*… the First Human Cases of Zika Virus Disease

- **Case #1** (1954) Nigeria: a 10-yr-old African female with fever and headache [MacNamara 1954]
- **Case #2** (1956) Nigeria: Experimentally-induced infection in a 34-yr-old European male, residing in Nigeria for 4 ½ months before inoculation; symptoms included headache and fever [Bearcroft 1956]
- **Case #3** (1964) Uganda: a 28-yr-old European male, residing in Uganda for 2 ½ months before illness; with headache, rash, and fever [Simpson 1964]
- **Cases #4, 5, 6** (1968) Nigeria: Zika virus isolated from 3 febrile children, aged 10 months, 2 ½ years and 3 years with no clinical details available [Moore 1975]

*and the rest is history…*


I would like to express my gratitude to Ms. Moira Rankin, Senior Archivist at the University of Glasgow Archives & Special Collections Library; to Dr. Andrew Haddow, United States Army Medical Research Institute for Infectious Diseases (USAMRIID), and to the Editor and editorial staff of the *Archives of Pathology & Laboratory Medicine* of the College of American Pathologist*s*