REVIEW

HIDEYO NOGUCHI'S RESEARCH ON YELLOW FEVER (1918-1928)
IN THE PRE-ELECTRON MICROSCOPIC ERA

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One of the low points in Hideyo Noguchi’s career as a pioneer medical microbiologist was his
investigations on yellow fever between 1918 and 1924 in Central and South America. His discovery that
spirochete Leptospira icteroides was the causative pathogen of yellow fever was discredited in 1927. This
paper evaluates the situation under which Noguchi conducted his experiments and assesses the causes
which might have resulted in his erroneous interpretation in the pre-electron microscopic era. Even 60
years after Noguchi’s untimely death, much remains to be known about the virulence of pathogenic
strains of yellow fever.

Introduction

Yellow fever still remains as an important cause of morbidity and mortality in 29 countries of
the tropical zone of Africa and in the forest areas of Amazon, Orinoco and Magdalena river basins
in South America1,2). 2230 cases of sylvatic yellow fever were reported to the Pan American Health
Organization between 1965 and 1983. During the same period, 2841 cases of yellow fever were officially
reported from African continent.

Hideyo Noguchi (1876-1928) spent his last ten years conducting research primarily on yellow fever.
Noguchi studied the epidemiology of yellow fever predominantly in the field areas of Central and
South America. However, Noguchi’s findings were disputed and later discredited in 1927, largely
due to the reports of Sellards, Stokes and Theiler3,4,5). When Adrian Stokes died from yellow fever
in Sept. 1927, Noguchi made his fatal expedition to Africa in Oct. 1927 and succumbed to the same
disease on May 21, 1928.

A few appraisals concerning Noguchi’s specific research areas such as human bartonellosis6) and
syphilis7) have appeared during the last few years. However, an evaluation of Noguchi’s contribu-
tion to yellow fever studies have not been attempted. Hence, this paper attempts to evaluate the situation under which Noguchi conducted his experiments and assesses the causes which might have resulted in his erroneous interpretation regarding the causative agent of yellow fever.

**Research in Central and South America**

Table 1 provides a chronology of Noguchi's research activities related to yellow fever research. Medical historians, Singer and Underwood summarized Noguchi's investigations on yellow fever in Central and South America as follows:

"Between 1918 and 1924, he went on four expeditions organized by the Rockefeller Commission to South America in an attempt to discover the cause of yellow fever. In 1919, while working in Guayaquil, Ecuador, he injected the blood of yellow fever patients into guinea pigs. The animals developed jaundice, haemorrhages from various organs and coma. In their blood, and after death in their livers and kidneys, he discovered a spirochaete which resembled that described by Inada and Ido. He called it *Leptospira icteroides*, and in the succeeding years, upto 1923, he obtained positive results with this organism in Pfeiffer's reaction, differentiated it by immunity tests from *L. icterohaemorrhagiae* and prepared from horses an immune serum which he used both prophylactically and therapeutically. It was then fairly widely recognized that *L. icteroides* was the cause of yellow fever in South America..."[8]

Between 1919 and 1924, Noguchi published 21 research papers in English on yellow fever[9-29]. Of these he was the sole author for 16 papers. He also summarized his investigations of this period in a 1925 review published in the *J. Trop. Med. Hygiene*[30]; and in 1927, also contributed a chapter on yellow fever to the reputed Cecil's *Textbook of Medicine*[31].

Biographer Eckstein[32] had focused on some of the factors faced by Noguchi in his South

<table>
<thead>
<tr>
<th>Year</th>
<th>Expedition location</th>
<th>No. of publications on yellow fever</th>
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<tbody>
<tr>
<td>1918</td>
<td>Ecuador</td>
<td>0</td>
</tr>
<tr>
<td>1919</td>
<td>Mexico</td>
<td>9</td>
</tr>
<tr>
<td>1920</td>
<td>Peru and Yucatan</td>
<td>5</td>
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<tr>
<td>1921</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>1922</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>1923</td>
<td>Brazil</td>
<td>0</td>
</tr>
<tr>
<td>1924</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1925</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1927</td>
<td>left for West Coast of Africa</td>
<td>1</td>
</tr>
<tr>
<td>1928</td>
<td>died in Accra, Gold Coast (presently Ghana)</td>
<td>0</td>
</tr>
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[N.B.] The 1925 and 1927 papers were reviews.
American expeditions, which could have led to the erroneous data and flawed interpretation of them. These include,

(a) Clinicians in South America had instructed Noguchi 'something was yellow fever that is not', and 'gave him bloods from the wrong disease or from the right and wrong indiscriminately'.

(b) Many blood collections in South America were obtained from 'convalescents who simply said they had had yellow fever, or whose physicians said they had'.

(c) Some blood collections 'were brought from the interior of the countries, collected under condi-

Table 2. Chronology of landmark events in yellow fever research and development in virology

<table>
<thead>
<tr>
<th>Year</th>
<th>Research in yellow fever</th>
<th>Development in virology</th>
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<tbody>
<tr>
<td>1881</td>
<td>Carlos Juan Finlay formulated the theory of insect transmission of yellow fever.</td>
<td>Iwanowski discovered tobacco mosaic virus (TMV)</td>
</tr>
<tr>
<td>1892</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1896</td>
<td>Giuseppe Sanarelli claimed isolation of <em>Bacillus icteroides</em> from yellow fever patients.</td>
<td></td>
</tr>
<tr>
<td>1898</td>
<td>Still widely held view was that yellow fever was spread by fomites, used by yellow fever patients.</td>
<td></td>
</tr>
<tr>
<td>1899</td>
<td></td>
<td>Beijerinck confirmed the presence of TMV.</td>
</tr>
<tr>
<td>1900</td>
<td>Walter Reed and James Carrol confirmed the role of <em>Stegomyia fasciata</em> mosquito in the transmission of yellow fever.</td>
<td></td>
</tr>
<tr>
<td>1915</td>
<td></td>
<td>Noguchi obtained a pure culture of vaccinia virus.</td>
</tr>
<tr>
<td>1918-24</td>
<td>Noguchi’s investigations on yellow fever in Central and South America; proposed <em>Leptospira icteroides</em> as the causative agent.</td>
<td></td>
</tr>
<tr>
<td>1927-28</td>
<td>Spirochete theory disproved by data from Africa reported by Adrian Stokes.</td>
<td>Invention of electron microscope by Ernst Ruska.</td>
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<tr>
<td>1931-32</td>
<td></td>
<td>Isolation of influenza virus.</td>
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<tr>
<td>1933</td>
<td></td>
<td>Stanley purified the TMV pathogen in paracrystalline form.</td>
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<tr>
<td>1935</td>
<td></td>
<td></td>
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<tr>
<td>1936</td>
<td>Production of yellow fever vaccine (17-D attenuated virus) by Max Theiler.</td>
<td>Bowden and Pirie reported that viruses were nucleoproteins.</td>
</tr>
<tr>
<td>1937</td>
<td></td>
<td>Nobel prize in chemistry for Stanley for his research on viruses.</td>
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<tr>
<td>1946</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1951</td>
<td>Nobel prize in medicine for Theiler for his contributions to yellow fever research.</td>
<td></td>
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</tbody>
</table>
tions that he (Noguchi) could not know”.

Another factor which could have contributed to Noguchi’s wrong deductions was also beyond his control. In that era (between 1918 and 1924) virology itself was in its early phase of development. As a reviewer pointed out in 1959, “It was not until the invention of the electron microscope that any conception of what a virus really looked like was obtained”\(^{33}\). And the scientific community had to wait till 1930s for the invention of electron microscope by Ernst Ruska\(^{34}\). Table 2 shows a comparative chronology of landmark events in yellow fever research and development of virology. It should be noted that Noguchi himself was not a stranger to virus research. In 1915, when the viruses were difficult to study due to their characteristic property of growing only within living cells, Noguchi was the first microbiologist to obtain a “pure culture of vaccinia virus by growing it in the testes of living rabbits and bulls”\(^{38}\).

**Research in the west coast of Africa**

When the news arrived on Sept. 19, 1927 that Adrian Stokes had died in Africa, Noguchi decided to pursue the investigations on yellow fever in the field spot in Africa. He had the motivation to proceed to Africa, since his theory that spirochete *Leptospira icteroides* is the causative agent for yellow fever had been refuted by the reports originating from Africa. It was Stokes who had provided the disputing report on yellow fever virus. Noguchi felt that his reputation as an attentive medical researcher was at stake. Though his wife Mary Dardis had opposed the idea, Noguchi made up his mind to travel to Africa. He was reported to have told his wife,

“‘What would you have me do! Would you have me sit here in the laboratory and perform test-tube experiments on bloods that somebody else collected five weeks before? No, I must go. I must work with my own bloods, fresh bloods from cases that I know about. I must satisfy myself...’”\(^{32}\)

There are only few documents to re-trace the period Noguchi spent in Ghana between Nov. 1927 and May 1928. Biographer Eckstein provides a description in his final chapter of 17 pages. But it lacks authenticating details. We have to rely on the cables and letters Noguchi sent to his wife and Dr. Simon Flexner. He first sailed to Liverpool, England from New York in the ship *Scythia* on Oct. 22nd 1927. From Liverpool, he switched to another ship and landed in the west coast of Africa in November.

Noguchi sent a cable from Accra to Dr. Flexner on Dec. 7th stating, ‘Work getting interesting; Everything alright. Noguchi’\(^{35}\). A similar message was repeated to Dr. Flexner in the second cable sent on Jan. 10th 1928. It read: ‘All well; work progressing. Noguchi’\(^{35}\). He mailed a letter dated March 23rd from Accra to his wife Mary. This letter provides some details about the research he was conducting then.

“‘...The work is heavy and I am hard at it to finish the job right this time. I believe I found the cause of yellow fever. This germ looks so ordinary... I have already used over 900 monkeys. We have to buy about 3 tons of food every day to feed them. No place else in the world can accommodate and take proper care of so many monkeys. Dr. Young is the head of the Institute where I have a room to fix up my laboratory. He is a Scottishman and is helping me in every way. He works with me now...’”\(^{35}\)

In a subsequent letter dated April 7th from Accra, to his wife, Noguchi indicated that his work was nearing completion.
"...it will be the end of May that I sail home from here. I am sorry to keep you waiting so long. But unless I do this my work will not be accepted by the British scientists and much more trouble will follow... I have now about five hundred monkeys to examine and am employing 40 to 50 men to take care of them. It is a nerve wracking work day and night but the end is in sight..."36)

On May 1st 1928, Noguchi also mailed a cable to his wife: ‘Am leaving here May 19 and hope to be home by middle June. Will let you know exact date and name of boat when decided...’35). This message could have been the last one Noguchi sent from Accra, before he died on May 21st 1928. Eulogies and editorials bemoaning the untimely death of Noguchi appeared in all the reputed biomedical journals such as Nature37), Science38), J. Amer. Med. Assoc.39), Lancet40,41), J. Trop. Med. and Hygiene42) and Japan Medical World43).

Evaluation

One commentator had noted in hindsight that the lack of success for Noguchi in yellow fever investigations could be traced to the fact that ‘he applied bacteriologic techniques to many virus diseases44). But at that point, little was known about viruses and how to tackle a virus pathogen itself was somewhat difficult and opinions were conflicting. The confusion regarding the status of yellow fever virus could be gleaned from some of Noguchi’s statements in his 1919 paper, entitled, ‘Mosquitoes in relation to yellow fever’17):

1) "The general impression (was) that the virus was a protozoan although nothing definitely objective was adduced in support of this view”.

2) "Some persons believe that the virus is ultramicroscopic, at least with the magnification possible at the present time”.

3) "The characteristics of the organism isolated from the yellow fever cases in the present investigation conformed with all the other known characteristics of the yellow fever virus...”

4) "According to my estimate a female stegomyia may take up 0.01cc or even less. Apparently a mosquito occasionally becomes infectious by taking up the one or two organisms which happen to be circulating in the peripheral blood of man, and it is these occasionally infected few which carry the disease. It is not difficult to realize the extent of ever increasing danger from a constant supply of the microscopic virus which an endemic center or an epidemic of yellow fever can provide”.

It became known that Noguchi confused the symptoms of leptoSpirosis (formerly called Weil’s disease) in the patients with that of yellow fever. In the pre-electron microscopic era, he couldn’t have identified the yellow fever causing flavivirus, which belongs to the arbovirus B-type. The yellow fever virus with a virion size of less than 50 nm couldn’t have been visible through phase contrast microscope. Even other human viruses (such as smallpox virus, mumps virus, measles virus, herpes simplex virus, rabies virus and influenza virus) were two or three fold larger in size than the yellow fever virus45).

To understand the status of virology in late 1920s, one should refer to the two Harvey lectures delivered by D’Herelle46 and Goodpasture47), in 1928 and 1929 respectively. In addition, Lwoff’s classic paper on the concept of virus48) as well as his Nobel lecture49) shed much light on the development of virology as a discipline. In 1928, when Noguchi died,

"...the nature of any filterable virus (was)... entirely unknown, and the group of virus diseases... (was) loosely hung together mainly by the thread of filterability of the active agents which cause
To be fair by Noguchi, one should accept that he conducted his research on yellow fever at a period in which virology itself was not defined and delineated. Only when Thellier found out in 1930 that mice were susceptible to yellow fever virus, if inoculated in the brain, it was possible to devise the needed laboratory methods to study the virus. Thellier succeeded in producing a yellow fever vaccine (17-D strain of attenuated yellow fever virus) in 1936 and was honored in 1951 with the Nobel prize in medicine for his contributions to yellow fever research. Later studies showed that the epidemiology of yellow fever in South America and Africa was not as simple as previously imagined. As shown in Fig. 1, the virus passes through three cycles (tree top cycle, jungle cycle and urban cycle) before becoming a notorious pathogen to humans. The reservoirs (hosts) and vectors of the virus in natural environment varies in the two continents.

Three reasons could be postulated for Noguchi’s dismal failure in yellow fever investigations between 1918 and 1924.

(i) The pathogen (yellow fever virus) itself: Noguchi conducted his studies in the era, when the virus could’t have been located and identified. With a particle size around 17-28nm, the yellow fever virus is among the smallest known. Later investigations showed that this virus “is quickly destroyed by many chemicals, including distilled water and physiologic saline solution in the absence of protein. It is ether and bile sensitive”.

(ii) Inadequate laboratory facilities for diagnosis of yellow fever: According to Kerr, “a definitive diagnosis of yellow fever in many mild cases is impossible to make on a clinical basis alone, and laboratory diagnostic procedures are required. Unfortunately, all but one of these require special facilities, available only in specialized laboratories”. It is doubtful that Noguchi had the luxury of such specialized laboratory in the South American countries.

(iii) Noguchi’s style of solitary research: Those who had known Noguchi as well as historians have commented on his style of solitary research. As Talbott observed, Noguchi’s approach to yellow fever investigations resembled that of “a harried mind in the hopes of making at least

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**Fig. 1. Comparison of life stages of yellow fever virus in South America and Africa**

[N.B.] Adapted from Ref. 51
one final contribution in microbiology”. The solitary publication record of Noguchi and some of the observations he had recorded in his papers lend credibility to this observation. For example, Noguchi had stated in one paper, “In a country where aestivo-autumnal parasites infest the population many times a malarial patient is brought to the Yellow Fever Hospital on the chance that the case is one of early yellow fever. All these cases were used for the experiments on the transmission of yellow fever without the loss of time which would have been caused by waiting for a diagnosis, for which a day or two might be required”[12]. In another paper, Noguchi wrote in the introduction: “To devote much time to microscopic examination during the period while the work with yellow fever patients was being carried on was impossible and also inadvisable, since it was a matter which could be taken up at a later date when more time is available”[15]. It is also plausible that if he had conducted his research with collaborators, the dubious results of locating one or few organisms of *Leptospira icteroides* in the blood of yellow fever patients could have been cross-checked.

However, when one reads Noguchi’s papers on yellow fever investigations in South America (with due allowance made to the time in which they were carried out), his experimental observations seems valid to a certain degree, even though he erroneously interpreted the causative organism as a spirochete. The eulogy in the *Nature* expressed a forthright evaluation: “The well established facts that the disease can be transmitted by an ultramicroscopic agent either by injection or through the mosquito are quite in harmony with his (Noguchi’s) thesis, for other spirochetes are known to have invisible phases”[37].

**Conclusion**

Passage of time as well as advances in research technology (especially the development of electron microscope in the 1930s) have rendered Noguchi’s data and deductions on yellow fever obsolete. But to gain a proper perspective, Noguchi’s research on yellow fever should be judged on the then available methods and facilities in the laboratory and field. As one eulogist wrote in the *Lancet*, ‘if genius is an infinite capacity for taking pains, then Noguchi was truly a genius”[41]. Whatever the errors in Noguchi’s data and inferences on yellow fever studies between 1919 and 1924, one has to appreciate his courage to re-investigate the problem personally in Africa at high risk.

Though 60 years had passed since Noguchi died, still yellow fever remains as a serious concern in Africa and in the forest regions of certain South American countries. During 1961-62, the yellow fever epidemic in Ethiopia involved 200,000 people of which 30,000 died[31]. Even now, according to Bres[2], (a former Chief of the Virus Diseases Unit of the WHO):

(a) Virulence of (pathogenic) strains and the competence of vectors (for yellow fever) still remain largely unknown.

(b) Knowledge on the physiopathology of the disease and its treatment is far from complete.

(c) Improvement of the vaccine (to yellow fever) is much to be desired.

**References**

35) Zaidan Hohjin Noguchi Hideyo Kinenko: Noguchi Hideyo Den, Akiba Insatsu Co., Tokyo, 289pp, 1963 (in
Japanese).

36) Photo exhibit, Hideyo Noguchi Memorial Museum, Inawashiro machi, Yama gun, Fukushima prefecture.