



Fame, Failure, and Yellowjack

The stories of Hideyo Noguchi and Max Theiler show how even major talents in science can flourish or be dissipated in the dogged pursuit of erroneous ideas

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A century ago, the Japanese bacteriologist Hideyo Noguchi became a member of the staff of the Rockefeller Institute in New York, a post he held until 1928 when he died at the age of 51. It's an appropriate time, then, to reflect on the career of this charming, dedicated yet obstinate man and on how it intersected with that of his contemporary, South Africa-born Max Theiler.

Theiler achieved international acclaim and a Nobel prize in 1951 after evolving one of the most successful vaccines ever developed, the 17D vaccine against yellow fever. Noguchi, despite other substantial attainments, strayed onto a false trail in pursuit of the organism responsible for the same disease. He even succumbed to yellow fever himself—committing, some have alleged, a microbiologist's *hara-kiri* once he suspected the truth about his failure.

But first Theiler. He was born in 1899 on a farm near Pretoria, the youngest child of veterinary bacteriologist Arnold Theiler. As a medical student at St. Thomas's Hospital, London, he did a minimal amount of work. Aided by monthly checks from his father, he preferred to spend his time in art galleries, at the theater, and reading H.G. Wells and Bernard Shaw.

Later, however, at the London School of Hygiene and Tropical Medicine, he happened to pick up a copy of *Infection and Resistance* by American bacteriologist Hans Zinsser. This fired his enthusiasm for science—a pursuit that contrasted sharply with the helpless, hopeless pill-giving he had seen at St. Thomas's and which he later called “hogwash.”

It was in London too that he met Oscar Teague from Harvard Medical School, who arranged an offer of a post there which Theiler

took up in 1922. Once at Harvard, Theiler became friendly with Zinsser and—this being in the midst of Prohibition—was soon exchanging recipes for home brewing.

And thus to yellow fever. Theiler found himself in the midst of a passionate debate about the cause of the condition. Two decades earlier, Walter Reed and James Carroll, working for a U.S. Army Commission studying the disease in Havana, Cuba, had produced evidence that a filterable virus was responsible. But this had failed to resolve the issue to everyone's satisfaction.

In particular, Hideyo Noguchi, working at the Rockefeller Institute, insisted that the culprit was a spirochete. Andrew Sellards, Theiler's boss, thought it was a bacterium, though not Noguchi's spirochete. Theiler, taking a stand unlikely to endear him to his new chief, argued that a virus must be responsible.

He was right. Soon, he had taken a major step forward by making the suspect virus grow for the first time in a laboratory animal, by injecting it into the brains of mice. Surviving an attack of the disease himself, he wrote up his work for *Science*, provoking hostile criticism from microbiologists at Harvard and elsewhere. He showed that the virus became attenuated for monkeys when grown in mice, and demonstrated that immune serum neutralized the organism. Then he was tempted away by a job at twice his current salary at the Rockefeller Foundation.

Wilbur Sawyer, the tempter, acted with great insight, because Theiler's work had poised him for two major initiatives. The neutralization test made it possible, through the screening of sera, to mount a worldwide survey of the disease's distribution. This was put in hand at once.

Secondly, it seemed likely that an attenuated



strain of the virus could be developed as a vaccine. Three years and many thousands of tissue cultures later, a flask labeled 17D yielded the virus that was to form the famous vaccine.

By 1940 field tests were complete, and over the next seven years the Rockefeller Foundation manufactured over 28 million doses. A few years later, according to Greer Williams (*Virus Hunters*, Hutchinson, 1950), the commuter who had been known to fellow travelers from Hastings-on-Hudson as "the man who lives next door to [baseball player] Alvin Dark" became "the Nobel prize-winner who lives next door to Alvin Dark."

All of which contrasts starkly with the tragic story of Hideyo Noguchi. Born of poor, illiterate parents in northern Japan, his ambition drove him, at the age of 23, to seek out Simon Flexner at the University of Pennsylvania. Disappointed not to be offered a job, he nevertheless found support in Philadelphia for work on snake venoms. He also made an unusually deep impression on colleagues at that time.

"He was sensitive, naive, generous to a fault, save where honors were concerned, a spendthrift in time, money and energy, a man of extraordinary drive and industry," writes Paul F. Clark in *Pioneer Microbiologists of America* (University of Wisconsin Press, 1961). "We appreciated his childlike simplicity, directness, and the fireball intensity of his purpose, and forgave his foibles and weaknesses."

Before Noguchi became interested in yellow fever, he conducted important studies in several disparate fields. He provided the first detailed description of hemolysis triggered by snake venoms, and of the damage caused to the endothelium of blood vessels, leading to hemorrhage and edema. His mark presaged the development in goats of an antidote to rattlesnake venom. And his meticulous studies resolved uncertainties about the role of *Bartonella bacilliformis* in causing both Oroya fever and *verruca peruana*.

However, it was yellow fever that proved to be Noguchi's downfall. The problem arose from his absorption, some might say obsession, with spirochetes, which he sought in a wide variety of different infections and tissues. Working at the same time as Theiler, he isolated one such organism which he believed to be the cause of yellow fever and named it *Leptospira icteroides*. However, Theiler and Sellards showed that this

was in fact indistinguishable from *Leptospira icterohemorrhagiae*, the agent of Weil's disease.

But Noguchi stuck to his guns. He continued to do so after the Rockefeller Foundation sent a team to the tropics and failed to find his spirochete in yellow fever patients. He even reaffirmed his view in 1927 after Adrian Stokes and colleagues, working in the Gold Coast (now Ghana), transmitted the disease to rhesus monkeys by using material passed through a bacterial filter.

Following the earlier report by Reed and Carroll, this was the definitive confirmation that the actual causative agent was a virus. Soon afterwards (even before the work was published), Stokes contracted the disease and died.

The following year, Noguchi left New York for Accra in the Gold Coast. By now very depressed, he announced: "I will win down there or die." For some months he searched, unsuccessfully, for his spirochete in yellow fever victims. Then he too died of the disease.

There's an odd tailpiece to this saga. In 1996 the government of Ghana issued a set of postage stamps to mark the 120th anniversary of Noguchi's birth. This prompted Torsten Wiesel, president of Rockefeller University, to write: "I appreciate the beautiful stamps celebrating the 120th anniversary celebration of the birth of Dr. H. Noguchi issued by the Ghana government. Perhaps you could inform me as to why the Ghana government decided to commemorate Dr. Noguchi."

As reported by S. S. Koide of the Population Council in New York (*J. Med. Biography* 8:97, 2000), the decision had been taken "because of Noguchi's undaunted devotion and endeavour in identifying the causative agent of yellow fever and in developing a vaccine against this disease in Accra during 1927-8. His presence there had a profound impact on the livelihood of the people in and about the Gold Coast. He exuded hope that inspired confidence that this scourge could be exterminated by executing a frontal attack on this microscopic enemy in a dramatic, 'blood and guts' charge."

One can only speculate as to whether Noguchi would have been pleased to receive this enthusiastic though largely unwarranted tribute. He might be happier to know that even today his name is remembered in the binomial attached to one of his beloved spirochetes, *Leptospira noguchii*.