

Yellow fever and Max Theiler: the only Nobel Prize for a virus vaccine

In 1951, Max Theiler of the Rockefeller Foundation received the Nobel Prize in Physiology or Medicine for his discovery of an effective vaccine against yellow fever—a discovery first reported in the *JEM* 70 years ago. This was the first, and so far the only, Nobel Prize given for the development of a virus vaccine. Recently released Nobel archives now reveal how the advances in the yellow fever vaccine field were evaluated more than 50 years ago, and how this led to a prize for Max Theiler.

Yellow fever disease has caused life-threatening epidemics throughout the last 500 years of human civilization. In the first half of the 20th century, the viral origin of the disease was identified, its means of spreading was clarified, and possible ways to prevent it were found. The concluding advance in these studies was Max Theiler's development of the 17D strain of attenuated virus, first reported in this Journal (1), which could be used as a live vaccine to save the lives of many millions of people. There was no question that the introduction of this vaccine was "to the benefit of mankind," as specified in Alfred Nobel's will, but how does Theiler's contribution compare with other advances that lead to vaccines against viral diseases that were introduced both earlier and later?

The aim of this article is to discuss the recently released Nobel archives to show how the advances in the yellow fever vaccine field were evaluated more than 50 years ago, and how this led to a prize for Max Theiler. The article will also discuss why the yellow fever vaccine has been singled out as the only viral vaccine hitherto recognized by a Nobel Prize, and the concept of "discovery," which was specified by Nobel as the one and only criterion of a prize in physiology or medicine.

The disease and the epidemics

Yellow fever is an infectious disease that leads to damage of many organs in

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the body, frequently due to severe bleeding. The liver is often affected, which eventually leads to jaundice, the symptom that gave the disease its name. For many hundreds of years, dreadful epidemics of yellow fever afflicted densely populated areas in countries with warmer climates. The way the disease spread remained enigmatic for centuries, and there were no means for rational intervention. This situation changed in 1900, when a commission headed by United States Army Surgeon Walter Reed used human volunteers to show that a mosquito vector, *Aedes aegypti*, was critical in the dissemination of the disease.

When Theiler arrived at The Rockefeller Institute in 1930, it was already the world's most important center of experimental yellow fever research.

In 1915, a Yellow Fever Commission was established by the International Health Board, which was funded by the Rockefeller Foundation, with the primary goal of eliminating breeding places for *Aedes aegypti* in areas where yellow fever was prevalent. This eradication effort was highly effective in many cases. In some settings, however, the disease remained, and this was not explained until the mid-1930s when new techniques were developed to study the virus and immunity against it. It then became clear that the natural reservoir of the virus was monkeys, between which the infection was spread



Max Theiler receives the Nobel Prize in Physiology or Medicine from the hands of His Majesty the King Gustaf Adolf VI on December 10, 1951. Photo provided by the Karolinska Institutet.

by various jungle-dwelling mosquitoes. The virus was occasionally transmitted from infected monkeys to humans by a range of different vectors, resulting in individual or small clusters of cases. If, however, these spurious cases of yellow fever (known as jungle or sylvan yellow fever) contacted larger human populations in urban areas, severe epidemics could develop in which the virus was then transmitted by *Aedes aegypti* from man to man.

With the development of a safe and effective vaccine by Theiler in 1937 (1–5), the urban form of the disease was eliminated, but epidemics of the jungle form of the illness still occur in the tropical belts of the Americas and Africa. It is estimated that approximately 200,000 cases and 30,000 deaths occur every year in nonimmunized populations. Much has been learned during the last 50 years about the complex interactions between different hosts, various mosquito vectors and strains of the virus, and the need for continued vaccination in certain settings (6).

The virus and possibilities for vaccine development

The Walter Reed Commission showed in 1902 that the agent that causes yellow fever passed through bacteria-proof filters (7). This was the first human infectious agent shown to be ultra-filterable,



Asibi, West African yellow fever survivor, who provided a blood sample from which the virus, used in extensive future research, was isolated. Photo from reference 2.

but it took time before the scientific community was convinced that the agent was truly a virus. Adrian Stokes and collaborators at the Rockefeller Foundation laboratory in Nigeria showed in 1927 that monkeys could be infected with material from humans with yellow fever (8). This was an important breakthrough, as the viral nature of the agent was confirmed using this animal system. The isolated virus was named the Asibi strain after the 28-year-old West African yellow fever survivor who provided the blood sample. This virus strain came to play a central role in the eventual development of a successful vaccine.

When Theiler arrived at The Rockefeller Institute in New York in 1930, it was already the world's most important center of experimental yellow fever research. Conditions for experimenting with monkeys had been established, and the basic properties of the virus had already been analyzed. Yellow fever virus turned out to be a relatively small virus (9). It readily lost its infectivity, but the presence of proteins stabilized this property. In present-day classification (10), the yellow fever virus is grouped together with more than 80 other viruses carried by arthropod vectors. The group is named flavivirus, from the

Latin *flavus* meaning yellow, a collective name appropriately derived from its most prominent member.

Max Theiler, the experimental scientist

Those who met Theiler give the same description of him as an exceptionally modest, gentle, and unassuming person. He was born in Pretoria, South Africa, in 1899 of Swiss-born parents and spent the first 20 years of his life there. After premedical training in South Africa, he went to England to do his medical training at St Thomas' Hospital in London. In 1922, he became a Licentiate of the Royal College of Physicians and a member of the Royal College of Surgeons, and in the same year he was awarded a Diploma of Tropical Medicine and Hygiene. Later that year, he went to the United States where he became first an assistant and later an instructor at the Department of Tropical Medicine at Harvard Medical School (Boston, MA).

The head of the department, Andrew Watson Sellards, had a particular interest in yellow fever. Following the success of the researchers at Rockefeller foundation, he and his collaborators—then working in Dakar, French West Africa—had isolated the virus in monkeys (11). Sellards brought this isolate, called the French strain, to his laboratory in the United States. In his early work at Harvard, Theiler showed that the spirochete *Leptospira icteroides* had no involvement in yellow fever (12). Although the Reed commission had already documented that the etiological agent of the disease was a virus, a theory that this spirochete was involved had been persuasively argued by Hideyo Noguchi (13). Theiler's findings conclusively disproved this. Theiler also did some preliminary comparative immunological studies of yellow fever viruses from West Africa and South America (14).

Theiler then propagated the French strain of virus in the brains of mice (15, 16). This was an important finding because it offered an alternative to the expensive and cumbersome use of monkeys to study the virus. Because of this contribution, the Rockefeller Foundation welcomed Theiler when he applied for

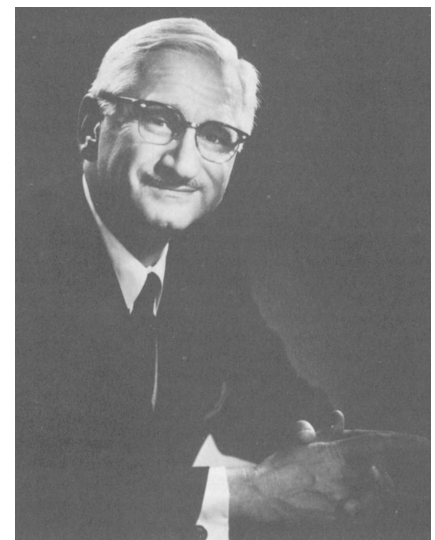
a position in its International Health Division (formerly the International Health Board) in 1930. Theiler enjoyed the environment of the Foundation and remained associated with it until he retired in 1964. He died in 1972.

Theiler's path of discovery

After Theiler's 1930 discovery that yellow fever virus can be propagated by passage in the mouse brain, he found that repeated passages in mice led to a progressive shortening of the incubation time and, importantly, a successive reduction of the pathogenicity of the virus in monkeys. Theiler then devel-

The stage was now set for a full attack on the problem of establishing a stable, effective, and safe attenuated virus.

oped a convenient test for measuring protective antibodies in mice (17). The technique also allowed a quantitative demonstration of the presence of antibodies in humans. This proved to be an important tool for mapping the epidemiology of infections and evaluating candidate vaccines. After Theiler's work on yellow fever, mice came into widespread use for studies of viruses that affect humans and animals.



Albert Sabin, the father of the live polio vaccine, who gave the only comprehensive nomination of Theiler for a Nobel Prize in 1948. Photo kindly provided by Samuel Katz.

During the 1930s, Theiler tried to grow the virus in tissue cultures. Together with Eugen Haagen, he eventually demonstrated the growth of mouse brain–adapted virus in chicken embryo cultures (18, 19). The stage was now set for a full attack on the problem of establishing a stable, effective, and safe attenuated virus. Theiler and collaborators first demonstrated that the attenuation of virus obtained by passages in mice was not sufficient. This diminished the viscerotropic properties of the virus, which are the main source of the symptoms associated with yellow fever, but the capacity of the virus to attack the brain increased. To get around this problem, attempts were made to use minimal doses of virus, but this approach also failed. Theiler and Whitman demonstrated that, paradoxically, lower doses of virus gave a higher frequency of encephalitis in monkeys (20, 21).

The critical experiments that solved this problem were performed by Theiler and his collaborators during 1935–1937 (1, 22, 23). Different virus strains with various properties were carried through several hundred passages in different kinds of tissue cultures and repeatedly tested for their neurotropic activity. The breakthrough came when the Asibi strain of virus—the first ever isolated—was passed repeatedly in minced chicken embryos from which the central nervous system had been removed. Between the 89th and 114th passage, a virus variant suddenly emerged that lacked both the viscerotropic and the neurotropic effects (1). Fortunately, the properties of this virus were stable, and its neurovirulence was not regained upon repeated passages in chicken embryo cultures containing brain material.

The first field trial with the new vaccine, started under the aegis of the Rockefeller Foundation in Brazil in 1938, was highly successful. And the continued use of more than 400 million doses for over 60 years of the 17D virus vaccine has proven it to be a remarkably safe and effective product. The World Health Organization guidelines regarding the vaccine have remained unchanged (24). Today, the vaccine is still produced using the original methods: it is passaged



Sven Gard, professor of virology at the Karolinska Institutet between 1948 and 1972. Photo provided by the Karolinska Institutet.

in embryonated chicken eggs and stored as a frozen homogenate.

The first deliberation by the Nobel Committee

The Nobel archives remain closed to researchers for 50 years, and hence the files on Theiler have only recently become available (25). Three kinds of material can be examined: the submitted nominations, the reviews made by professors of Karolinska Institutet, and the recommendations by the Nobel Committee for Physiology or Medicine to the College of Teachers. Candidates considered to be prize-worthy were listed, and the candidate(s) recommended for the prize by the majority of the committee was presented without any comments on the basis of the committee's decision.

But one ingredient was still needed for Theiler to reach his goal. That ingredient was luck.

To be considered for a Nobel Prize in a certain year, an individual must be nominated before January 31 of that year (26). Max Theiler was first nominated for the Nobel Prize in Physiology or Medicine in 1937 by Friedrich K. Kleine of the Robert Koch Institute for Infectious Diseases (Berlin, Germany) for his work on yellow fever in mice. These findings, however, were not interpreted by the committee to have

sufficient originality to motivate further consideration of Theiler for the Prize. The next nomination came in 1948, with the development of the yellow fever vaccine as the core of the proposal. The nominator in 1948 was Albert Sabin, a respected authority in pathogenesis of viral diseases who could well appreciate the challenge of establishing an attenuated strain of virus to be used as a vaccine. Sabin had also worked at the Rockefeller Institute for Medical Research between 1935 and 1939 and, being at the same campus, had firsthand insight into the critical advances made in Theiler's laboratory. Later, Sabin became the father of the live polio vaccine that has successfully eliminated polio from many parts of the world.

Sabin's nomination was very detailed, covering some six pages, and included reprints of Theiler's most important papers. The Nobel Committee was seemingly impressed by the nomination and asked Sven Gard (my former mentor), who had become professor of virus research at the institute the same year, to make a preliminary investigation. Gard, who would later become a pioneer in polio vaccine research, was highly qualified to make such an evaluation. He knew Theiler's work well from the 10 months he spent in his laboratory in 1939 as a visiting scholar, during which they worked on a mouse poliomyelitis-like virus called Theiler's virus (27, 28).

After an exhaustive preliminary review, Gard concluded that Theiler's work would be prize-worthy if a further investigation showed that it was Theiler, and not Wray Lloyd, Theiler's close friend and colleague who died shortly after publication of their work, who had conceived and planned the critical experiments. Gard had the proper contacts in Theiler's laboratory to get advice on this priority issue. In a brief supplementary review, Gard firmly concluded that Theiler was the leading scientist in the team and declared his work on yellow fever prize-worthy.

Continued deliberations by the Nobel committee

In 1948, the Nobel Committee agreed with Gard that Theiler's contributions



Hilding Bergstrand, professor of general pathology and pathological anatomy 1924–1952, vice-chancellor (rector) of the Karolinska Institutet 1942–1952, and chairman of the Nobel Committee for Physiology or Medicine 1947–1952. Photo provided by the Karolinska Institutet.

were prize-worthy. But the prize that year was instead awarded to Paul H. Müller “for his discovery of the high efficiency of DDT as a contact poison against several arthropods.” Theiler’s next nomination was in 1950. This time, Antonia Salvat Navarro from Granada, Spain, nominated him together with another leading yellow fever researcher, Wilbur A. Sawyer. Gard, who by that time was an adjunct member of the Nobel Committee, wrote a two-page analysis primarily to define Sawyer’s role in vaccine development. Before Theiler developed his 17D strain, Sawyer and his collaborators tried to immunize humans with a previously isolated neuroadapted strain of virus from mice together with injections of human convalescent serum. This provided some immunity, but the procedure was difficult to control and not practically useful. This procedure was used, however, to successfully protect people working with the virus in the laboratory. Gard’s conclusion was that Sawyer’s contribution was not of sufficient magnitude and quality to be included in a prize for the yellow fever vaccine. In its summarizing recommendations to the College of Teachers in 1950, the Nobel Committee again concluded that Theiler’s work was prize-worthy. However, the majority of the

Committee members recommended that the prize be given to Philip S. Hench, Edward C. Kendall, and Tadeus Reichstein “for their discoveries relating to the hormones of the adrenal cortex, their structure, and biological effects.” Still, four of the thirteen members, Professors Nils Antoni, Hilding Bergstrand (the chairman), Gard and Arne Wallgren, recommended that the prize instead be shared by Frank MacFarlane Burnet, for his discoveries of methods that make cells resistant to certain virus infections, and Max Theiler, for his discovery of methods to vaccinate effectively against yellow fever. Burnet was one of the prominent figures in the field of virology at the time, but he would have to wait until 1960 to get his Nobel Prize. The prize Burnet was eventually awarded, however, was not in virology but in immunology and was shared with Peter B. Medawar for their discovery of immunological tolerance. In 1950, the College of Teachers supported the majority opinion of the committee, and Theiler had to wait one more year.

Early on January 31, 1951, the last day when prize nominations could be submitted for that year, there was no proposal of Theiler. But a brief nomination referring to the evaluations of the preceding year was submitted later that day by the chairman of the committee, Vice-Chancellor of the Karolinska Institutet and Professor of Pathology Hilding Bergstrand. Such a last-minute nomination is not unprecedented in the Nobel Committee work, but it is generally given by the committee’s secretary.

Bergstrand not only made the “moonlight” nomination of Theiler, he was also, somewhat surprisingly, the one who performed the evaluation. In the beginning of his four-page review, he declared that he did not have anything to add to Gard’s description of the process of developing the yellow fever vaccine. Instead, he highlighted the importance of the availability of the vaccine, stating that it was the practical results that should give Theiler an advantage in the competition with other candidates for the 1951 prize.

He also expressed the hope that Theiler’s success would serve as an encouragement to other scientists trying to develop vaccines against important human virus infections.

In the report to the faculty, all but two of the committee members (Gard was not included that year) agreed with the recommendation that Theiler should be awarded the 1951 prize. The two dissenters recommended that it be given to Selman A. Waksman, but this did not happen until the following year when he was awarded the prize “for his discovery of streptomycin, the first antibiotic effective against tuberculosis.” In 1951, the college of teachers agreed with the majority of the Committee and awarded Theiler the prize.

Theiler received his Nobel Prize based on only three nominations (the early 1937 nomination did not concern the creation of the 17D strain vaccine). By contrast, Waksman had

He showed a capacity for a systematized approach and persistence in action—personal qualities that are essential to good science.

accumulated 39 nominations over six years before winning the prize. Out of the three nominations Theiler received, only the one in 1948 was detailed. Thus, Theiler owes special thanks to Sabin, who submitted this qualified proposal. These two scientists must have met many times in the late 1930s when they were working at the Rockefeller Institute of Medical Research and had the same dining room privileges. But it seems less than likely that they developed a close friendship. It is hard to imagine two more diametrically different personalities.

What is a discovery?

Nobel made some interesting and important distinctions when he specified the three prizes in natural sciences in his last will. For physics, he specified that the award be given for “a discovery or an invention”; for chemistry,

“a discovery or an improvement”; but for medicine or physiology, he stated exclusively, “a discovery.” By definition, therefore, all prizes in physiology or medicine that have been given reflect the identification of a discovery. But how can the concept of “discovery” be defined and distinguished from more consequential and applied contributions? And again, why has only one of the many viral vaccines been recognized, considering their enormous humanitarian impact, which is truly in accordance with Nobel’s specification “to be of benefit to mankind”?

Why was Theiler's contribution considered a discovery?

This question was answered in part in a recent article (29) discussing the award of the 1954 Nobel Prize in Physiology or Medicine to John Enders, Thomas Weller, and Frederick Robbins. These researchers demonstrated that poliovirus could grow in nonnervous tissue, thereby refuting the persistent and incorrect dogma that the virus was strictly neurotropic. This unexpected discovery spearheaded the subsequent isolation of many important human viral pathogens and paved the way for the development of effective vaccines. The important contributions of Salk, Sabin, and others in the development of the polio vaccine can be speculated to have been considered derivative, as no additional discovery was needed, and thus not prize-worthy. Why, then, was Theiler’s contribution considered a discovery?

In Gard’s preliminary investigation in 1948 there are some—in my opinion surprisingly harsh—comments on this matter. It reads:

“Theiler can not be said to have been pioneering. He has not enriched the field of virus research with any new and epoch-making methods or presented principally new solutions to the problems, but he has shown an exceptional capacity to grasp the essentials of the observations, his own and others,

and with safe intuition follow the path that led to the goal. The practical importance of Theiler’s work needs not to be discussed. It is to a large part thanks to him that the worst scourge of the tropical belt has now been rendered harmless.”

In a milder form, Bergstrand returned to this issue toward the end of his laudatory speech delivered at the prize ceremony (30):

“The significance of Max Theiler’s discovery must be considered to be very great from the practical point of view, as effective protection against yellow fever is one condition for the development of the tropical regions—an important problem in an overpopulated world. Dr. Theiler’s discovery does not imply anything fundamentally new, for the idea of inoculation against a disease by the use of a variant of the etiological agent which, though harmless, produces immunity, is more than 150 years old.”

One may ask whether the expression “discovery does not imply anything fundamentally new” is a contradiction in terms.

The problem Theiler faced was clearly defined; a live vaccine needed to be developed. But which approach should be taken? How useful were the available techniques and what was the need to develop new ones? Theiler was good at adapting existing techniques and pioneering the development of new approaches. His mouse encephalitis model, which later came to be widely applied in virology, and his modifications of the crude tissue culture techniques of the day are examples of this. His idea of growing the virus for hundreds of passages in chick embryo cultures with and without brain material was ingenious. In the critical tissue culture experiments, he showed a capacity for a systematized approach and persistence in action—personal qualities that are essential to good science. The experimental systems he used were highly complex, and hence the outcomes of the experiments were unpredictable. Here, both his intuition and his capacity to appreciate the relative significance of the



Max Theiler. Photo provided by the Nobel Foundation.

many different observations he made came into play.

But one ingredient was still needed for Theiler to reach his goal. That ingredient was luck. Louis Pasteur’s famous dictum, “in the field of observation, chance only favors the prepared mind,” promptly comes to mind. Theiler was lucky that passage of the Asibi strain in chick embryos without central nervous systems suddenly changed its nature and lost both its viscerotropic and neurotropic properties, but still retained its capacity to replicate and induce an immune response. It was also fortunate that the properties of the attenuated virus turned out to be stable. It was the fulfillment of all these conditions that allowed Theiler to make what must be concluded to be a true discovery.

To conclude, it would of course be of considerable interest to learn what Theiler himself thought about his contribution and the fact that it was recognized by a Nobel Prize. Some insight into this can be gained from the interview conducted by Dr. Harriet Zuckerman (31), the author of a book on American Nobel laureates (32). Discussing the conditions for good science, Theiler emphasized the role of a hunch and also of luck. Being a man of paradoxes, he commented on his achievements in two contradictory ways. On the one hand, he stated that he had not done anything fundamental and that he did not

have any background for making essential theoretical contributions. On the other hand, he made it clear that it was he alone who took the essential initiatives to the experiments that led to the development of the vaccine. In his view, if anyone should get a credit for the vaccine it should be him and him alone. No one else needed to be included. Thus, although he was not a man to boast of his own achievements, he probably, in his humble way, knew his worth.

It may be appropriate to let Theiler himself have the last word. In his speech at the prize award banquet, he used the following generous and gracious formulations (33):

“I like to feel that in honouring me you are honouring all the workers in the laboratory, field and jungle who have contributed so much, often under conditions of hardship and danger, to our understanding of this disease. I would also like to feel that you are honouring those who gave their lives in gaining knowledge which was of inestimable value. They were truly martyrs of science, who died that others might live. And, finally, I would like to feel that in honouring me you are honouring The Rockefeller Foundation under whose auspices most of the modern work on yellow fever has been done—a gesture from one great foundation to another—both having the ideal of benefiting mankind throughout the world. Thank you.”

The access to the Archives of the Nobel Committee for Physiology or Medicine of the Karolinska Institutet, the Rockefeller Archive Center, the Library of The American Philosophical Society, and a transcript of an interview with M. Theiler by Harriett Zuckerman at Columbia University Oral History Office are gratefully acknowledged.

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