Thomas H. Weller

The Nobel Prize in Physiology or Medicine 1954

Biography

Thomas Huckle Weller was born at Ann Arbor, Michigan, on June 15th, 1915. He was educated at the public schools there, and later at the University of Michigan, where his father, Carl Vernon Weller had an appointment in the Pathology Department of the Medical School. Entering this University in 1932, T. H. Weller graduated in 1936, taking the A.B. degree. Early in life he had shown an interest in natural history, and this no doubt influenced him during his University life in the direction of medical zoology. He was also influenced in this direction by Professors G. R. LaRue, and A. E. Woodhead and, after his graduation, he worked for two summers at the University of Michigan Biological Station under Professors L. J. Thomas and W. W. Cort on the parasites of fish. In 1937 he was awarded the M.S. degree for this work.

In 1936, however, he had entered the Harvard Medical School in Boston and there he was given, by Drs. E. E. Tyzzer and Donald L. Augustine, facilities for research in the Department of Comparative Pathology and Tropical Medicine. His experiences under the direction of these two distinguished parasitologists, whose outstanding discoveries in protozoology and helminthology are well-known, must have been very valuable.

The course of much of Weller's later work was, nevertheless, influenced by the fact that he was accepted, in 1939, as a tutorial student by Dr. J. F. Enders, who introduced him to the field of virus research and to the study of tissue-culture techniques as a means of studying the causes of infectious disease. In 1940 he took his M.D. degree and began his clinical training at the Children's Hospital in Boston. His work here was, however, interrupted by military service in the Second World War, for he joined, in 1942, the Army Medical Corps and was stationed at the Antilles Medical Laboratory in Puerto Rico for 32 months. There he was Head of the Departments of Bacteriology, Virology and Parasitology and attained the rank of Major. He then returned to the Children's Hospital, Boston, for a further year of clinical training and, in 1947, he joined Dr. Enders in the organization of the new, Research Division of Infectious Diseases at the Children's Medical Centre.

In 1949 he was appointed Assistant Director of this Division and subsequently was appointed Instructor, Assistant Professor, and then Associate Professor in the Department of Comparative Pathology and Tropical Medicine of Harvard Medical School. The department was renamed and transferred to the Harvard School of Public Health. In July 1954, he was appointed Richard Pearson Strong Professor of Tropical Public Health and head of the Department at the Harvard School of Public Health.

In his researches, Weller was interested, partly in the helminth parasites of man, and partly in virology. In helminthology he contributed to the literature on the nematode *Trichirella spiralis* and also to that on the schistosome trematodes which cause schistosomiasis of man, his contributions including methods of cultivating the schistosomes *in vitro* and modifications of methods for the recovery and counting of the eggs of these parasites.

In virology his studies of varicella and herpes zoster resulted in his isolation for the first time of the viruses responsible for these diseases, and also in the development of diagnostic tests and in the demonstration that the same virus apparently causes both these diseases. In 1955 he also isolated the virus which causes cytomegalic inclusion disease in infants and, after working for five years on these diseases, he was able to show that the human foetus, while it is in the uterus, is particularly susceptible to attack by these viruses and that, if the foetus survives attack by them, the infant is often born with severe damage to its brain which causes mental retardation and cerebral palsy. Weller's subsequent work has included studies of the Coxsackie viruses as causes of epidemic pleurodynia and on the behaviour of *Toxoplasma gondii* in tissue culture. He is also studying the propagation *in vitro* of the viruses that cause varicella and herpes zoster.

In addition to the appointments already mentioned, Weller served, from 1953 till 1959, as Director of the Commission on Parasitic Diseases of the American Armed Forces Epidemiological Board.

In 1945 he married Kathleen Fahey and they have two sons, Peter Fahey and Robert

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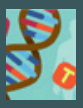
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Andrew, and two daughters, Janet Louise and Nancy Kathleen.

From *Nobel Lectures, Physiology or Medicine 1942-1962*, Elsevier Publishing Company, Amsterdam, 1964

This autobiography/biography was written at the time of the award and first published in the book series *Les Prix Nobel*. It was later edited and republished in *Nobel Lectures*. To cite this document, always state the source as shown above.

Addendum, August 2005

My addendum features my work in academic tropical medicine at Harvard. When I arrived at Harvard Medical School in 1936, the Department of Tropical Medicine had disappeared; for financial reasons it had been fused with the Department of Comparative Pathology which was located in Building E-2 of the Harvard Medical School (HMS). The head of Tropical Medicine, Dr. Richard Strong, had retired; only a senior associate, Dr. Watson Sellards, remained active. The main task of the fused department was to teach a required course in medical parasitology for second year HMS students. As a student with a classmate, Wallace Sorenson, I investigated the prevalence and associated symptoms of pinworm infections in Boston school children; the results were published in the New England Journal of Medicine. One summer was spent studying malaria in Florida at Rockefeller training centers. My interest and training in tropical medicine was the basis for my army assignment in 1942 to a laboratory in Puerto Rico that was responsible for malaria control at our numerous bases throughout the Caribbean.

After the war in 1946 major organizational changes occurred in the medical-health area at Harvard. Former General Steve Simmons was appointed by President Conant as dean of the newly independent Harvard School of Public Health (HSPH). The hybrid department of comparative pathology and tropical medicine was renamed the department of Tropical Public Health (TPH) and was transferred to the HSPH. In 1953, Nathan Pusey became president of Harvard. Dean Simmons died in July 1954 and was replaced by Dr. John Snyder. In July 1954 I was Pusey's first professorial appointee being named head of TPH. I was pleased that my appointment occurred before the Nobel award.

When in 1954 I was appointed head of the Department of Tropical Public Health at the Harvard School of Public Health (HSPH), a position held until 1981, academic responsibilities occupied a major proportion of my time. With the support of training grants from the National Institutes of Health I was able to expand the academic faculty by adding Dr. Eli Chernin, a protozoologist, Dr. Steve Pan, a parasitologist, Dr. Ed Michelson, a medical malacologist, and Dr. Andrew Spielman, a medical entomologist. These individuals served throughout my tenure, providing a harmonious multidisciplinary teaching group. In the School of Public Health we usually attracted over 80 students to our basic course required for a MPH degree. Smaller numbers attended courses in malariology, malacology, medical entomology, and the clinicopathology of tropical diseases. In each subject the ecological and epidemiological aspects were emphasized. Seventeen doctoral degrees were awarded and usually each faculty member had one or two post-doctoral research fellows. Each year we offered a course in medical parasitology required for all second year medical students that involved three afternoons a week for a month. When Dr. John Snyder was appointed Dean of the Public Health School in 1954 the Department received excellent support, a situation persisting until his retirement in 1971.

In 1954, the new Department occupied three floors in the E-2 wing of the Medical School. An immediate objective was to plan and to raise money to rehouse the Department in new buildings, a goal achieved in 1969 when we occupied three floors in two new HSPH buildings.

My research efforts continued to utilize tissue culture techniques to study viral and parasitic diseases. Studies on the varicella-zoster viruses were continued and definitive papers on the cultural and immunologic characteristics of viruses from the two diseases were published in 1958.

In 1957 we recorded the first recovery of cytomegaloviruses (CMV) from living children with cytomegalic inclusion disease and demonstrated that such children continued to excrete viruses in their urine for many months. The viruria provided a useful diagnostic approach and indicated why the infection could spread rapidly in groups of preschool children. Evidence was obtained that the cytomegaloviruses constituted a closely related but antigenically heterogeneous group of agents. Like other herpes viruses the cytomegalviruses remained latent in infected individuals, becoming active when the host was immunosuppressed as an organ transplant recipient or by an HIV viral infection. Information indicating that the CMV was the major cause of damaging viral congenital infections was obtained by many virologists.

With the rapid utilization of tissue cultures, knowledge of the damaging congenital rubella syndrome led many investigators to attempt to isolate the etiological virus. We investigated four different outbreaks of German measles in schools with negative results. Then in 1960, my ten year old son, Robert, developed a febrile illness that had some characteristics of German measles but was much more severe than the usual case. I was

worried and inoculated roller cultures of human amnion cells with his urine. I observed the cultures microscopically for a longer period than customary and on the 26th day after innoculation observed peculiar rounding of scattered cells with refractile bodies in the nucleus and cytoplasm. The cytopathic changes progressed and the causative agent could be readily subcultured. The question was "had we finally isolated the rubella virus"? I enlisted the collaboration of Dr, Franklin Neva, then a faculty associate. Fortuitously at that time, we learned of a rubella outbreak at the Phillips Exeter Academy. Franklin was able to collect urine specimens from two Exeter cases and from a Harvard student with rubella. Each specimen produced cell changes similar to those seen in my son's cultures.

We then found that we were not alone in the field. Beginning in 1961 a group at the Walter Reed Institute of Research in Washington had isolated viruses from cases of rubella using cultures of monkey kidney cells. No cytopathic changes were seen but application of a viral interference method, originally developed by David Tyrrell in England, demonstrated that the rubella virus was present. With the help of Drs. Albert Sabin and Joe Smadel we exchanged viruses with the Washington group and found the isolates identical. Dr. Smadel arranged that papers from each group be published "back to back" in the October 1962 issue of the Proceedings of the Society of Experiment, Dr. Charles Alford on the viral aspects of the congenital rubella syndrome.

In 1963 in recognition of my isolation of the CMV and rubella viruses I was greatly pleased by the award by Harvard of the George Ledlie prize, an award given every two years to the Harvard faculty member considered to have made the major contribution to human welfare.

Research on the etiology of rubella was my final major study in the area of virology. Since our initial paper in 1949 on the cultivation *in vitro* of the polio viruses the utilization of tissue culture procedures by many virologists had resulted in the isolation of hundreds of new viruses and in the development of vaccines for the major viral diseases of children. When we received the Nobel Prize in 1954 Professor Sven Gard stated that tissue cultures will do for virology what Koch accomplished when he revolutionized bacteriology by the development of culture media. Events have proven the truth of his prediction.

The disease schistosomiasis was a major research focus of TPH. One goal was the development of techniques for the control of the snail vectors. A search for specific pathogens of snails failed but it was determined that the introduction of certain nonvector snails would displace the vector snails. Working with doctoral candidates or post-doctoral fellows the growth *in vitro* of schistosomules of *S. mansoni* was accomplished. A specific circulating antigen elaborated by the worms was demonstrated in the blood and urine of infected animals. This finding has stimulated other workers to develop sero-diagnostic tests, thus providing an alternative to classic diagnostic tests based on the demonstration of eggs of the worms. One objective, the cultivation of the cells of schistosomes, although pursued many years with hundreds of different media, was not achieved.

Although time consuming, service on national and international health agencies was a scientifically valuable experience. Such included membership of committees of the World Health Organization, the Pan American Health Organization, and the International Health Organization of the Rockefeller Foundation. Consultative assignments included meetings in St. Lucia, Trinidad, Egypt, Thailand, South Africa, Saudi Arabia, and Kuwait. With the valuable support of Dr. Peter Williams of the Wellcome Trust, a research and training center for young physicians and scientists interested in tropical medicine was established in a rural area of Salvador, Bahia, Brazil where Chagas disease and schistosomiasis were highly endemic. Initiated in 1972 this project was active through 1983.

In 2004 I published an autobiographical volume: Weller, Thomas H., *Growing pathogens in tissue cultures. Fifty years in academic tropical, medicine, pediatrics, and virology*, pp. 1-292. Science History Publishers, Canton, Mass. Dr. Eli Chernin in 1985 published a historical manual on TPH: Chernin, Eli, *Tropical Medicine at Harvard. The Weller Years, 1954-1981. A personal memoir*, pp. 1-95. Harvard School of Public Health.

Thomas H. Weller died 23 August, 2008.