NATIONAL ACADEMY OF SCIENCES

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1915–2008

A Biographical Memoir by
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From Thomas H. Weller, *Growing Pathogens in Tissue Cultures,* Science History Publications/USA (2004), © Boston Medical Library. Bachrach Studio Photograph.

THOMAS H. WELLER

June 15, 1915–August 23, 2008

BY KENNETH MCINTOSH

THOMAS H. WELLER WAS A PHYSICIAN who devoted his life to the investigation of viral and parasitic diseases, making major research contributions to the former and fostering, through his teaching, administration, and advocacy, advances of global importance in the latter. His lifelong devotion to research stemmed in part from early experiments on parasitic infections of fish in Michigan, near Ann Arbor, where he grew up. Much of his subsequent career was spent as Richard Pearson Strong Professor and chair of the Department of Tropical Public Health at the Harvard School of Public Health, where he taught and nurtured students from many countries and infected them with his enthusiasm for attacking the problems of world health, particularly those related to infections with parasites. Despite this career-framing interest in parasitology, his most important scientific accomplishments were, paradoxically, in the field of virology. In an extraordinary set of fastidiously conducted experiments over the course of 15 years, carried out with his mentor John Enders, Weller cultivated for the first time the mumps virus, poliovirus, and varicella zoster virus in tissue cultures; during the same burst of productivity, he independently (albeit simultaneously with other investigators) grew and characterized both cytomegalovirus and rubella virus.

For his work on poliovirus Weller, Enders, and Frederick Robbins were awarded the 1954 Nobel Prize in Physiology or Medicine. This accomplishment paved the way for development of the inactivated and live polio vaccines, the subsequent elimination of poliomyelitis from the Western Hemisphere and Europe, and the near eradication of polio from the world. The prize was awarded jointly to all three investigators since, although Enders was clearly the senior scientist and the inspiration behind the work, the ideas for and the conduct of the experiments were joint, and as recently described in a review of the Nobel records by Erling Norrby and Stanley Prusiner, the Nobel Committee never considered anything but a prize to all three scientists *(Ann. Neurol.* 61[2007]:385-395).

EARLY LIFE

Thomas Huckle Weller was born on June 15, 1915, in Ann Arbor, Michigan, the son, nephew, and grandson of physicians. His father became the chair of the Department of Pathology at the University of Michigan Medical School and was an important influence on his son. The world Tom Weller grew up in was filled with wildlife, and he became an avid birdwatcher and nurtured a young crow as a pet, teaching him to come when called and to protect the house from strangers. As a biology major he ran a bird-banding station while attending the University of Michigan, where he wrote his first published report on the recapture after 12 years of a previously banded blue jay, the longest recapture interval described at the time.

During his undergraduate summers at the University of Michigan, he worked at their biological station where he first developed a fascination with parasites. In the course of his summer studies he described the remarkable male-to-female sex ratio of perch in Douglas Lake (99 to 1) and discovered

and described a new nematode in the intestines of these same perch. He received a master of science degree along with his bachelor's degree in 1936.

Following family tradition and continuing his interest in biology, he applied for Harvard Medical School, entering in the fall of 1936. During the summer following his second year, he spent two months studying at the Rockefeller Foundation malaria laboratory in Tallahassee, Florida. His work there convinced him that he should devote his life to the study of infectious diseases and, in particular, diseases of importance in the developing world. When faced with a requirement for a study block in public health (usually fulfilled by doing a sanitary survey of a community in the vicinity of Boston), he received permission to perform, with a fellow student, a study of pinworms in children, finding a strikingly high prevalence in children consecutively sampled from the clinics at Children's Hospital Boston, describing for the first time that most infected children were asymptomatic. The work was published as a two-author paper in the New England Journal of Medicine (1941), and he received his M.D. degree in 1940 magna cum laude in recognition of this research.

During his last year at Harvard Medical School, he spoke with bacteriologist Hans Zinsser in an effort to find a laboratory position and was referred to John Enders, who was working with vaccinia virus in the Zinsser laboratory. Enders was trying to grow vaccinia in vitro, using several of the rapidly evolving forms of tissue culture available at the time. Weller was interested in growing parasites in tissue culture and started work with Enders during his final year of medical school.

Weller's next few years were very much influenced by the war in Europe. He started his internship at Children's Hospital with six months in the hospital's bacteriology laboratory, where he shared the duty with Fred Robbins. The next

six months were spent working under Sidney Farber in the hospital pathology laboratory. His major contribution during this rotation was to import tissue culture techniques into the pathology laboratories, and to try to culture varicella virus on his own. Pearl Harbor was bombed during the last month of his pathology rotation, and he enlisted the next spring after only a few months as a clinical intern.

Weller began his military service with two in-depth courses in tropical public health taught by the nation's most prestigious experts, rounding out his education in parasitology and preparing him for both his military duties and his subsequent career. He spent the next three years in the army's infectious disease laboratories in Puerto Rico, where the major health problems were venereal diseases, malaria, and schistosomiasis. By methodically implementing imaginative and careful public health measures, he and his colleagues were able to reduce the prevalence of both parasitic diseases in the Caribbean region during the course of the war. He also published several technical papers and with Gustave Dammin a large and wide-ranging survey of parasites in Puerto Rican Selective Service conscripts (1945), outlining for the first time in such detail the distribution of *Schistosoma mansoni*, hookworm, ascaris, strongyloides, and several other parasites in over 19,000 young men coming from all parts of the island. The entire experience was formative in that he obtained from it a lifelong obsession with tropical diseases, their study, and their control. He was demobilized as a major in December 1945 and returned to Children's Hospital to complete his clinical training, rejoining Enders's laboratory very shortly after it had moved from its quarters at the Medical School under Hans Zinsser to Children's Hospital in January 1947.

Thus began what must be one of the most remarkably successful set of laboratory experiments in history. Weller first showed that mumps virus grew and produced hemagglutinin in suspended cultures of chick embryo skin and muscle and under Enders's tutelage followed this with influenza virus, which was shown also to replicate and produce hemagglutinin in these cultures. The Lansing strain of poliovirus (which grew and was pathogenic in mice) had been imported into the laboratory at a time when they were studying the capacity of Coxsackie viruses to produce paralysis in mice, and on Weller's initiative it was put into tissue culture. The experiment was an afterthought in another unsuccessful experiment to try to grow varicella in a human embryo culture system: there were a few extra culture vials available, and it was decided to try poliovirus in one of them, along with parallel cultures inoculated with control fluid. The fluids harvested from the polio-inoculated cultures consistently produced hind-leg paralysis in mice, and the group of Enders, Weller, and Robbins went on to characterize in detail the growth of all poliovirus types taken not just from laboratory samples but from patients' fecal specimens as well. The work, started in 1948, was published in a set of seven papers by all three authors in varying order, the first in Science in 1949 and the last in the *Journal of Immunology* in 1952. It was for this work that Weller, Enders, and Robbins received the Nobel Prize in 1954.

Although the first growth of poliovirus had been in suspended cultures, it became clear that cells grown in test tubes rotated slowly on a roller drum represented a more versatile culture system, with greater ability to maintain the cultures over long periods, and more rapid production of the "cytopathic effect" (a term coined by Enders) that became a characteristic of each virus. The development of

antibiotics simplified handling of the cultures and allowed the inoculation of bacterially contaminated clinical samples for the isolation and propagation of viruses. Weller went on to show, in work published in 1953, that varicella could be grown in this system from fluids removed from skin vesicles, and that it could be passaged indefinitely using whole cells rather than supernatant medium. In work that he later told one of his coworkers, Joseph Waner, he considered his finest scientific accomplishment, he showed that the viruses from chickenpox and herpes zoster were identical using every characterization system available at the time (and later as well). In further studies he grew and characterized both cytomegalovirus and rubella virus, the former in 1957 in an effort to isolate what he thought would prove to be *Toxoplasma gondii* from an infant with an undiagnosed congenital infection, the latter in 1962 and published simultaneously with a group of investigators from the Bureau of Biologics at the Food and Drug Administration.

Weller's work with cytomegalovirus and rubella was done in his own laboratory after he had moved to the Harvard School of Public Health. It is interesting that growth of both viruses in tissue culture was accomplished at about the same time and independently by other workers and characteristically Weller shared his data with these investigators and published his work simultaneously and with the open recognition that it was a shared accomplishment. His group was the first to recover cytomegalovirus from living patients, and he and his students and colleagues did much to advance our knowledge of the pathogenesis of both infections.

HARVARD SCHOOL OF PUBLIC HEALTH

Although immersed in laboratory work with viruses, Weller retained his early fascination with parasitic diseases and took an active role in the teaching of tropical infectious

diseases at the Harvard School of Public Health, starting as early as 1948. He received his first professorial appointment at that school in 1949, quickly rose in rank, and was named the Richard Pearson Strong Professor of Tropical Public Health and chair of the Department of Tropical Public Health in 1954, the same year he received the Nobel Prize. He remained department chair for 27 years, until 1981, and became Professor Emeritus in 1985.

These were years of enormous expansion in the Harvard School of Public Health. While much of this was due to the increasing budget of the National Institutes of Health, the bulk of the school's physical growth was based on private philanthropy. Weller was clearly important in this process, using his position, charm, Midwestern connections, and commitment to public health and particularly tropical public health, to raise money from the Wellcome Trust, the Rockefeller Foundation, the Given Foundation, the Kresge Foundation, and several wealthy individuals to support the bricks-and-mortar expansion of the school and its transformation into the overall structure it has today.

TEACHING

From his first academic appointment Weller felt that teaching was a core mission. In terms of sheer time and energy the teaching of parasitology to students of public health and medical students was a central focus of his life from the late 1940s until his retirement. At the Medical School he supervised a teaching block that was very popular (known at the time I took it in 1960 as "worms"), with heavy faculty commitment and extensive hands-on laboratory work. It was a course that consistently received accolades from the students, so much so that it caused occasional embarrassment to the administration of the Medical School, being taught entirely by a team from the School of Public Health.

This embarrassment must have been acute when Weller was asked by the Medical School class of 1963 to give the class day address at the time of their graduation, an address that was published in the *New England Journal of Medicine* with the title "Questions of Priority" (1963).

At the School of Public Health his teaching was at all levels and included many foreign physicians who came for degree programs and returned to positions of responsibility in their home countries. Under his leadership the Department of Tropical Medicine was responsible for many core courses, and when he or a member of his department directed a course, in contrast with today's practice, it was expected that all those who had signed up to teach would attend all the lectures, and that all would take part in tutoring in laboratory exercises. His doctoral students included Leonardo Mata, who became one of the world's most respected authorities on malnutrition and infection in children, and Debhanom Muangman, who was subsequently dean of the Faculty of Public Health at Mahidol University in Thailand. His research students included Charles Alford, James Hanshaw, Jerome Klein, and many others who pursued research and educational careers in the field of infectious diseases. Watching his ex-students and ex-junior colleagues rise to positions of leadership was one of the great satisfactions of his career.

PARASITOLOGY

Weller's commitment to research in parasitology was lifelong, starting with nematodes in perch caught in Michigan lakes, continuing in medical school and the army, and throughout his academic life. His parasitic contributions were wide-ranging and important, and unlike many professors he frequently left his name off papers when he thought his coworkers had in fact done most of the actual work.

His early studies of fish parasites in Michigan and pinworms in Boston, as well as his experience in the U.S. Army during World War II were described above. After joining the Enders laboratory he continued to introduce occasional experiments on parasites among his many studies of multiple viruses. After moving into his own space at the School of Public Health, he was able to set up a laboratory program devoted to parasitologic investigation, as well as develop field programs on both schistosomiasis and trypanosomiasis.

As chair of the Department of Tropical Public Health he was in a position to frame the questions that he considered important. Because of his interest in schistosomiasis, the biology of snails, their major nonhuman host, was one of the areas he identified. At the beginning of his tenure he recruited Edward Michelson, a young scientist with a recent Ph.D. from Harvard in the biology of snails (malacology), to set up a laboratory for the study of this external host of all the schistosomes affecting man. This laboratory became enormously productive over the next decades. In a similar vein he later recruited Andrew Spielman, a superb entomologist, to study mosquitoes and other insect vectors of human disease. Essentially everyone in the department except for small groups working with cytomegalovirus and rubella worked on parasitic diseases (or related fields such as malacology and entomology), including amoebiasis, toxoplasmosis, leishmaniasis, trypanosomiasis, babesiosis, filariasis, toxocara, malaria, strongyloides, and of course, schistosomiasis.

Weller with his students and colleagues developed and refined tests for an antigen from *Schistosoma mansoni* that circulated during active infection. But his most sustained laboratory effort in schistosomiasis was to explore the cultivation of the parasite in vitro, building on his seminal work with viruses in tissue culture. He expended a huge effort in working out the constituents of nutrient media for the growth,

maturation, and maintenance of schistosomules, schistosome eggs, whole worms, and other forms of the parasite. These were tedious trial-and-error experiments that would have been out of the question for an investigator who had not already made his reputation. While the work resulted in numerous publications, it did not lead to the sort of breakthroughs that he seemed to be seeking.

The field studies were the product of a fruitful association with the Wellcome Trust and a carefully nurtured collaboration with the Federal University of Bahia in Salvador, Brazil, lasting from 1972 until 1985. With the close cooperation of Brazilian faculty members, Weller and his colleagues, most of whom were trained in his department, set up a field station in the town of Castro Alves, where both *Schistosoma mansoni* and *Trypanosoma cruzi* were endemic. This venture led to a substantial number of publications (not all of which listed Weller as an author) outlining the natural history of Chagas' disease and Manson's schistosomiasis, both of which were successfully controlled in the study population through various public health measures.

Interestingly, according to James Maguire, who worked closely with him both in Boston and in Brazil, Weller despite the "ivory tower" location of his office and laboratory was frequently consulted on thorny clinical problems in tropical medicine by ex-students and acquaintances all over the world. He responded to these consultations with the greatest care, and according to Maguire (a noted clinician), displayed uncanny clinical acumen in reaching solutions to problems that had stumped some of his most seasoned colleagues.

SPOKESPERSON FOR TROPICAL PUBLIC HEALTH

Weller sat on or chaired innumerable committees and was centrally connected to many of the advances in public health. He seemed to have at one time or another his finger

in most of the pies worldwide that advised on or created research policy in tropical infectious diseases and tropical public health: the Commission on Parasitic Diseases of the Armed Forces Epidemiologic Board (1953-1959), World Health Organization's Committee on Medical Research (1967-1970), Centers for Disease Control's National Advisory Council (1968-1972), Pan American Health Organization Advisory Committee on Medical Research (1970-1981), National Institute of Allergy and Infectious Diseases National Advisory Council (1977-1980), and numerous shorter-lived committees and commissions, including several committees at the National Academy of Sciences, expert panels of WHO, and multiple committees of the American Society of Tropical Medicine and Hygiene (president, 1964). Through his many connections he played a direct role in the control of schistosomiasis on the Caribbean island of St. Lucia. He took his committee responsibilities seriously and functioned both to direct research funds toward the study of neglected diseases of the developing world and to keep the health disparities between the two worlds in the government and academic spotlight to the greatest extent that he could.

HONORS AND LEGACY

Weller received many honors in addition to his sharing the Nobel Prize in Physiology or Medicine in 1954. In 1952 he received the E. Mead Johnson Award of the American Academy of Pediatrics, in 1973 the Weinstein Award from the Cerebral Palsy Association, and in 1980 the Bristol Award from the Infectious Diseases Society of America. He was elected to the National Academy of Sciences in 1964, and became an honorary fellow of the Royal Society of Tropical Medicine and Hygiene in 1987. He delivered one of the Harvey Lectures in 1957 and held innumerable named lectureships from 1957 until 1989. He received honorary degrees from the

University of Michigan, Gustavus Adolphus College, Lowell University, and the University of Massachusetts.

Weller's legacies are many. His contributions to the development of the polio vaccines and the near eradication of polio have to be at the very top of the list. Then, there are the many advances in the control of varicella, including the vaccine, which not only can prevent chickenpox but also can lessen the chances of severe zoster in the elderly. Mumps and rubella are now both controlled through vaccines, and it seems likely to be only a question of time before cytomegalovirus will similarly be tamed. As a department chair at Harvard a large segment of the credit for the expansion of the School of Public Health belongs to him. In the field of parasitology, in addition to elucidating important parts of the natural history of Chagas' disease and fostering extensive research on the snail vector of schistosomiasis, his earnest and encouraging voice was to a large extent responsible for our current increased awareness of these "great neglected diseases of mankind." His many students carry forward the torch that he lit, in the United States and in all corners of the world.

I AM GRATEFUL TO JOSEPH WANER, JAMES MAGUIRE, AND PETER WELLER for their personal contributions and the time they spent in conversations with me about Thomas Weller's life and accomplishments. I also leaned heavily on Thomas Weller's autobiography, *Growing Pathogens in Tissue Cultures: Fifty Years in Academic Tropical Medicine, Pediatrics, and Virology* (2004), as well as the short monograph *Tropical Medicine at Harvard: The Weller Years, 1954-1981: A Personal Memoir* by Eli Chernin (Harvard School of Public Health, 1985).

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