H. Boyd Woodruff

1917–2017

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
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NATIONAL ACADEMY OF SCIENCES

HARAROLD BOYD **WOODRUFF**

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Elected to the NAS, 1998

By Joan Wennstrom Bennett and Arnold L. Demain

H. Boyd Woodruff, a founding father of the discipline of *biochemical engineering*, made many significant contributions to industrial microbiology. His intensive search for antimicrobial agents in soil, as opposed to those formulated in laboratories, played an essential role in the research leading to both the 1952 and the 2015 Nobel Prizes in Physiology and Medicine (Bennett, et al., 2017).

Woodruff earned a bachelor's degree (Phi Beta Kappa) in soil chemistry from Rutgers University in 1939, followed in 1942 by a Ph.D. from Rutgers under the mentorship of the noted microbiologist Selman Waksman. Before completing his Ph.D. Woodruff went to work at the Merck Institute of Therapeutic Research, remaining at Merck in increasingly responsible positions. After his retirement in 1982, he and his wife, Jeanette, founded Soil Microbiology Associates. They traveled widely, continuing his life-long search for soil microorganisms capable of producing new drugs.

Harold Boyd Woodruff was born on July 22, 1917 on a farm in Bridgeton, New Jersey, and he was always proud of his farming origins. Throughout his life he enjoyed telling about the way he supported himself during his college years by keeping a large flock of chickens on campus and selling their eggs. While an undergraduate at Rutgers University, he majored in soil chemistry, courted his future wife, Jeanette Whittier, and graduated Phi Beta Kappa in 1939.

Boyd's hard work, personal charm, and strong intellect had come to the attention of Selman Waksman, a top microbiologist on the faculty of Rutgers' Soil Microbiology Department, who offered him a stipend to help fund his further education. Waksman's favorite organisms were a group of filamentous bacteria called actinomycetes, and Boyd was charged with finding practical applications for them. In one of his early projects Boyd was directed to take soil, infuse it with a bacterial pathogen, and try to enrich the

H. Boyd Woodruff, 1941 at Rutgers.

mixed population of bacteria in the soil to find ones that produced an antagonistic substance. Within less than a year, Boyd had found a new strain, which was named *Actinomyces antibioticus* (now called *Streptomycetes griseus*), that produced an antimicrobial substance, later named actinomycin (Waksman and Woodruff, 1940, 1941). Although actinomycin proved too toxic to serve as a useful antibiotic, it later found application as an investigative tool in molecular biology and as a chemotherapeutic agent for the treatment of Wilms tumor.

Not long after, Boyd purified another compound from an actinomycete, which was named streptothricin (Waksman and Woodruff, 1942). Streptothricin was active against both Gram-positive and Gram-negative bacteria, and colleagues showed that it was effective against a contagious form of bovine abortion caused by *Brucella abortus*. Unfortunately, later human trials revealed delayed renal toxicity, and the compound could not be developed for clinical use, a major disappointment for Boyd. Nevertheless, his successful isolation of actinomycin and streptothricin was instrumental in changing the research direction of the entire laboratory. New visiting scientists and graduate students in the Waksman laboratory were assigned to antibiotic research. Moreover, the soil enrichments and screening approaches first developed by Boyd were refined by others and then embraced across the laboratory, allowing two other graduate students, Albert Schatz and Elizabeth Bugie, to find streptomycin, the first drug effective against tuberculosis (Schatz, et. al, 1945).

Even before finishing his graduate studies Boyd joined the Merck Institute of Therapeutic Research in Rahway, New Jersey, working side by side at the bench with Norman Heatley, a young chemist from Oxford, England. Their charge was to develop fermentation methods for scaling up the production of penicillin. Boyd received his Ph.D. from Rutgers in 1942 (Woodruff, 1942) and immediately was hired by Merck to continue penicillin research. He proved to be good at executing his charge. He matched his scientific insights with an ability to work effectively with multidisciplinary teams. He played a key role in improving the penicillin production process. Previous workers had grown the *Penicillium* mold in solid cultures. The Merck group perfected methods for growing the fungus in “deep tank” fermentations, which was the way traditional brewers make beer. Similar conditions were optimized for streptomycin, and eventually, many other valuable microbial natural products. Along the way, Boyd led teams that established an emergent new subdiscipline—biochemical engineering.

Jackson Foster, Alexander Fleming and Boyd Woodruff- penicillin consultation, Merck, 1945.

By the early 1950s Boyd was the head of Merck's microbiology department, with nearly 100 people working under his supervision. Streptomycin, the first effective drug for treating tuberculosis, was a great success for Merck. Moreover, Selman Waksman, Boyd's mentor, won the Nobel Prize in Physiology or Medicine in 1952. Around this time came another opportunity for using microbial products to treat disease. Karl Folkers, a chemist at Merck, and workers in England crystalized the factor from liver extracts that had been used to treat pernicious anemia. This factor is now called vitamin B_{12}. Hypothesizing that microbes might make the same or similar factors, Boyd led a team that found that several bacteria could produce the anti-anemia factor, including a strain of *Streptomyces griseus*. The demand for vitamin B_{12} was so great that fermenters five times the size of those used for antibiotic production were developed.

Boyd's executive responsibilities at Merck increased, and by 1957 he was Director of the Department of Microbiology and Natural Products Isolation. By 1969 he was Executive Director for Biological Sciences. The Merck group under his direction expanded into the production of bacterial polysaccharides for use in a pneumococcal vaccine, and to amino acid fermentations for lysine and glutamic acid.

Boyd's intellectual clarity and generous nature were essential components of his leadership skills. By all measures of success, he should have been content. Nevertheless, the confines of being an industrial scientist were chafing to him. He considered taking a job at an Ivy League university, but in 1973 his company countered with an offer he could not refuse. He was asked to establish a new laboratory for Merck Sharp & Dohme Research in Japan, serving as its executor administer. For nearly five years he and Jeanette lived half the year in Tokyo, where he was responsible for identifying new Japanese medicinal discoveries. Working with Tojo Hata, president of the Kitasato Institute, and Hata's successor, Satoshi Ōmura, one of their targets was to study 3000 different microbes. These were screened for activity against nematodes. An unusual culture, orig-

H. Boyd Woodruff and Norman Heatley in post World War II discussions at Merck, possibly 1970s.

inally isolated from a golf course on the Izu Peninsula of Honshu, the main island of Japan, produced an anti-helminthic complex. The producing species was named *Streptomyces avermitilus*. A new class of broad-spectrum anti-parasitic agents named avermectins was isolated (Ōmura, et al, 1977). A derivative of one of these, marketed under the name Ivermectin, eventually passed human clinical trials and was used internationally in the treatment of onchocerciasis ("river blindness"), as well as other worm infestations and scabies. In addition, other Japanese products brought to the American market under Boyd's direction included a children's chicken pox vaccine, a urinary tract disinfectant, and pepsin for heartburn.

In 1982, after 40 years at Merck, Boyd retired and formed his own company, Soil Microbiology Associates, Inc. With Jeanette as his working partner, he focused on isolating microbes from unusual soil habitats such as volcanic lakes. They coupled their soil isolation strategy with specialized screening procedures, eventually collecting over 5500 actinomycete cultures and finding a number of new natural products with potential as anti-viral, anti-cancer, anti-inflammation, and anti-ulcer candidates (Woodruff, 1999).

Just as Boyd had worked within Merck to bring microbiology into the pharmaceutical industry, which had previously been driven by synthetic organic chemistry, he also worked within several professional societies to bring industrial microbiology into a discipline previously dominated by clinical and food perspectives. When the Society for Industrial Microbiology (now the Society for Industrial Microbiology and Biotechnology) was founded in 1949, he was an early member, later serving for two years as president (1954-1956). He also helped create a place for industrial microbiologists within the American Society for Microbiology (ASM). Until the antibiotic revolution, most microbiologists had studied organisms that cause disease and thus had a strong clinical orientation. He served for many years as treasurer of ASM and was instrumental in founding their journal *Applied Microbiology* (now *Applied and Environmental Microbiology*), serving as its first editor-in-chief (1953-1962). In 1981 he was the first industrial microbiologist to write an introductory chapter for the *Annual Review of Microbiology*. This biographical essay is worth reading today. It describes the excitement of Boyd's front-seat participation in the golden era of microbiology discovery, and it also is a model for how to share credit for discoveries with colleagues (Woodruff, 1981).

Boyd served on the boards of the American Type Culture Collection, the American Society of Microbiology Foundation, the executive board of the U. S. Federation for Culture Collections, the board of trustees of *Biological Abstracts*, and as president of the Theobald Smith Society. He received many academic honors over the course of his career, including the Charles Thom Award of the Society of Industrial Microbiology and honorary membership in ASM, the Kitasato Institute, and the Japanese Society for Actinomycetes. In 1998 he was elected to the National Academy of Sciences, and in 2011 he received the NAS Award for the Industrial Application of Science.


2016 Woodruff and Bill Campbell at Merck (Campbell had been awarded Nobel).

Boyd was a particularly loyal alumnus of Rutgers University, which had given him financial support when he was a penniless student, and where he "first became aware that soil is not simply dirt but a teeming mass of microbial life" (Woodruff, 1980). Late in life he and Jeanette established several scholarships at Rutgers using the well-husbanded funds from his portion of the patent royalties on streptomycin. On the occasion of the 100-year anniversary of the founding of the Department of Soil Microbiology, he was instrumental in creating a small museum to honor Selman Waksman. In 2004 Rutgers rewarded his allegiance and philanthropy when he was inducted into the Rutgers University Hall of Distinguished Alumni.

Well into his nineties Boyd remained intellectually acute and physically active. Together, he and Jeanette were avid travelers, regularly visiting Japan and other international destinations. At home, they enjoyed sunsets at the Jersey Shore, supported the local food bank, and were active in their church. When Jeanette died in 2015, after 72 exceptionally happy years of marriage, Boyd was never quite the same, although he did derive enormous satisfaction when he learned that his colleagues Satoshi Ōmura (Kitasato Institute) and William Campbell (Merck and Drew University) shared the 2015 Nobel Prize in Physiology or Medicine for their work on Ivermectin. He died on January 19, 2017, at his home in Watchung, New Jersey, at the age of 99.

Boyd and Jeanette are survived by two sons, Brian and Hugh, their daughters-in-law Sandra and Sandria, and grandchildren Lauren, Andy, and Ashley. Boyd's global circle of friends and collaborators remember him for his passion for industrial microbiology, his deep-seated integrity, and his unfailing personal decency.

Jeanette and Boyd Woodruff on holiday, circa 2014.

Woodruff – 99th birthday.

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