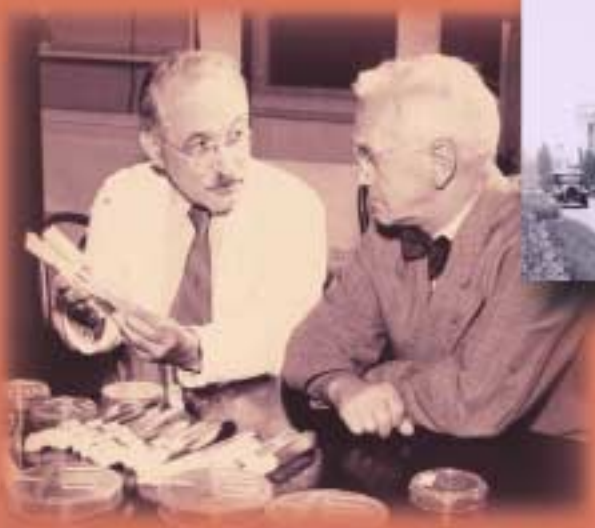
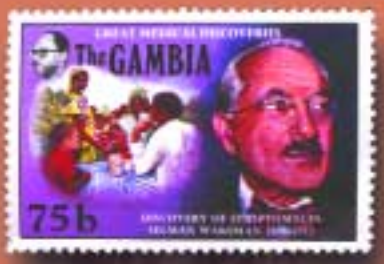
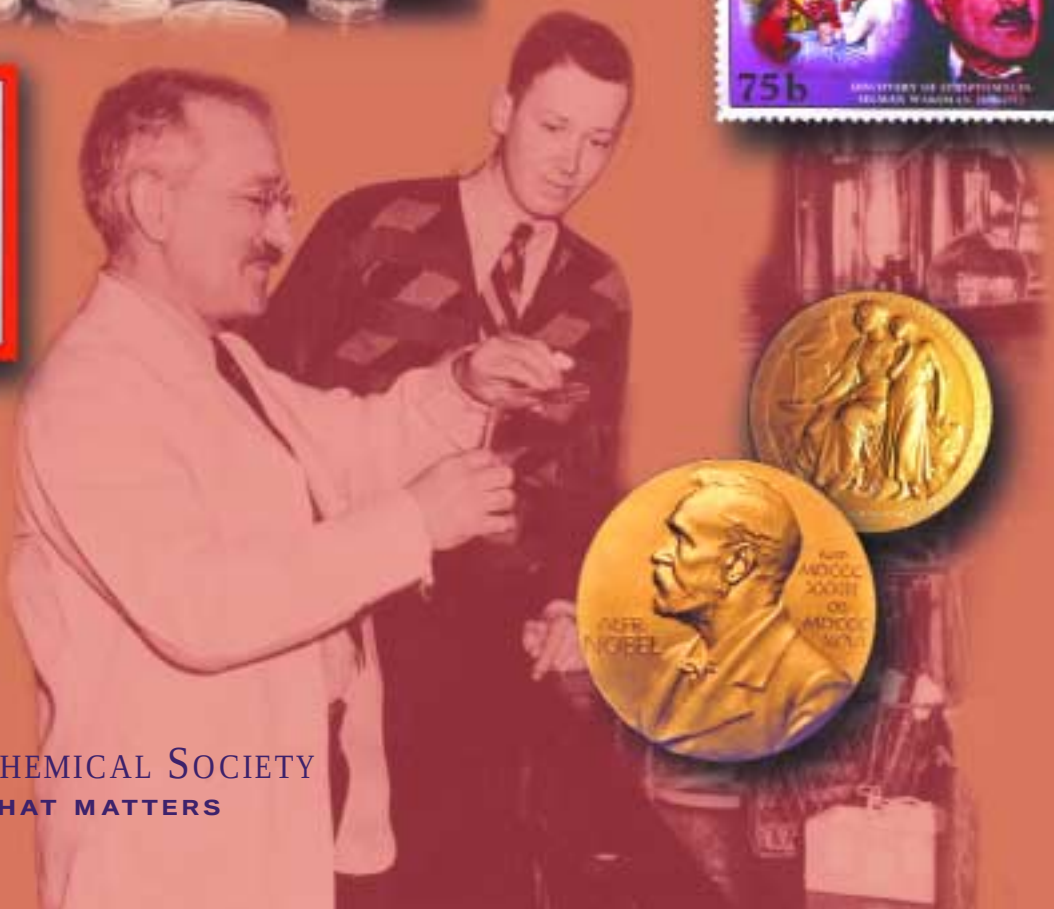
Selman Waksman and Antibiotics

May 24, 2005

A National Historic Chemical Landmark







AMERICAN CHEMICAL SOCIETY

SCIENCE THAT MATTERS

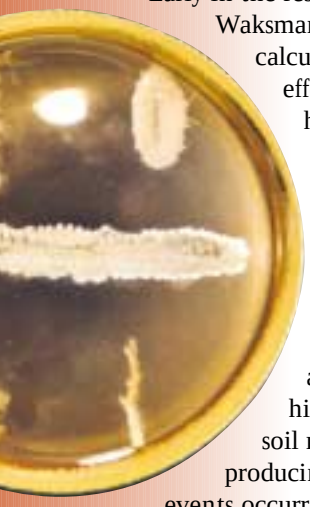
"The Lord hath created medicines out of the earth; and he that is wise will not abhor them." *Ecclesiasticus*, xxxviii, 4

antimicrobial

Actinomycetes and the search for antibiotics

Selman Waksman called his autobiography *My Life with the Microbes*, a fitting title since his enduring fame rests on the discovery of streptomycin, an antimicrobial agent produced from actinomycetes. These are a group of filamentous microbes, closely related to bacteria in size and physiology but similar to fungi in structure.

Waksman first became interested in actinomycetes in 1915 as a student at Rutgers. For the next several decades, he studied their occurrence and abundance in soil and their taxonomy. Early in the research at Martin Hall, Waksman and his students calculated the antagonistic effects that actinomycetes have on bacteria and fungi, establishing that perhaps half of all the actinomycetes had the capacity to inhibit the growth of other microorganisms.



Still, in the 1920s and most of the 1930s, his research focused on soil microbes, not disease-producing organisms. Two events occurred in 1939 that forced a change in his approach. One was the start of World War II, which suggested the need for new agents to control infectious diseases and epidemics. The second event was the work of René Dubos, one of Waksman's former students, who isolated tyrothricin, which destroyed disease-producing bacteria. Dubos showed that it was possible to find bacteria that inhibited the growth of other bacteria. Waksman was spurred by this breakthrough to search for actinomycetes active against pathogenic bacteria.

Waksman approached the search for antibiotics in a novel and systematic way, unlike the chance discovery of penicillin by Alexander Fleming, who observed an accidental contamination of a bacterial pathogen by an airborne mold. Waksman and his students screened cultures by looking for growth inhibition zones surrounding single colonies of a series of isolated soil microbes on agar plates. They then proceeded to test the inhibition on specifically targeted pathogenic bacteria. This was painstaking work, as thousands of cultures of different microbes were isolated and then tested for antibacterial activity. Waksman's screening protocols yielded about twenty new natural inhibitory agents. In fact, it was Waksman who suggested what has become the common term — antibiotics — for these therapeutic agents.

The first agent isolated was actinomycin, discovered in 1940 by Boyd Woodruff, a Waksman graduate student. Actinomycin was active against a broad range of bacteria and even showed promise of attacking a tuberculosis strain, but it proved too toxic for therapeutic use. Two years later, Woodruff isolated streptothricin. The researchers were excited about streptothricin because initial tests showed that it was not toxic to animals. However, pharmacology studies demonstrated that streptothricin had a delayed toxic effect.

The partial success of streptothricin indicated that Waksman and his students were on the right track. They needed to find a variant that inhibited pathogenic organisms — the easy part — without actually killing the host — the hard part. The breakthrough came in 1943, when Albert Schatz joined the team and isolated two strains of *Steptomyces griseus* that produced streptomycin, which attacked bacteria resistant to penicillin.

The trials of streptomycin

Even more exciting to the researchers was that streptomycin exhibited *in vitro* activity against *Mycobacterium tuberculosis*, the Great White Plague. To further test streptomycin's effectiveness, Waksman contacted two medical investigators at the Mayo Clinic, William H. Feldman and H. Corwin Hinshaw, to perform tests with guinea pigs. Waksman was able to supply the Mayo Clinic with sufficient samples because of a prior agreement he had reached with Merck & Company under which the giant pharmaceutical company provided partial funding, chemical assistance, and experimental animals for pharmacological evaluation of antibiotics. In return, Waksman assigned Merck any patents resulting from research in his laboratory. Should any of the patents prove commercially successful, Merck was to pay The Rutgers Foundation a small royalty.

Feldman and Hinshaw began *in vivo* tests in 1944 with streptomycin supplied by Merck and within two months reported to Waksman that two tubercular animals receiving the antibiotic looked well. In September, when a 60-day *in vivo* test of a large sample was completed, Feldman noted that none of the animals had tuberculosis. In 1945, clinical trials confirmed the animal results.

The tests proved that streptomycin was the first effective chemotherapeutic treatment for tuberculosis. It also was effective against a host of other diseases: typhoid fever, cholera, bubonic plague, tularemia, urinary tract infections, and others. As early as 1945, Waksman, realizing that streptomycin would be an important antibiotic, became uncomfortable with the agreement giving Merck exclusive rights to the drug, so he persuaded the company to negotiate a new agreement under which patent rights were assigned to Rutgers.

Because it attacked a wide spectrum of diseases, including tuberculosis, streptomycin almost immediately began generating huge profits, and Rutgers assigned a small part of the royalties to Waksman. Given all the

money and fame attached to the discovery of streptomycin, it is no surprise there would be some ruffled feathers. Nonetheless, it came as a shock when Albert Schatz sued requesting Waksman to cease claiming he was the sole discoverer of streptomycin and asking for an accounting of the royalties.

Selman Waksman, right, conferring with Albert Schatz

Schatz believed he was co-discoverer of the drug as he had performed the basic laboratory work in its isolation. His name was listed first on the original paper reporting the discovery and second on the patent. Waksman naturally believed he was most responsible for the discovery since it came through his screening program which previously yielded actinomycin and streptothricin. Waksman was convinced that Schatz, who worked in the laboratory for three months in 1943 after being released from the army, had made only a minor technical contribution to the discovery.

In December 1950 the case was settled. Schatz was recognized as co-discoverer of streptomycin. Under the agreement Schatz was to receive three percent of the royalties paid to the Foundation, with ten percent going to Waksman and another seven percent divided among all who participated in the early work leading to the development of streptomycin. (Waksman later reduced his share to five percent) Although he agreed to the settlement, Waksman always considered 1950 the "darkest" year of his life.

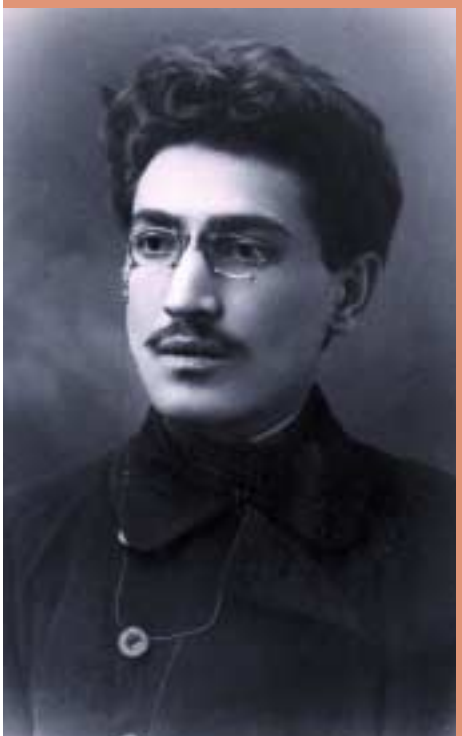
Selman Waksman: From Tsarist Russia to New Jersey

Selman Abraham Waksman was born and raised in the small town of Novaya-Priluka in Ukraine in 1888. The black earth of the steppes was highly productive, and while the Waksmans were town dwellers, the fertility of the soil no doubt influenced the young boy's later career choice.

His father, Jacob, was a pious man who earned a modest living by renting out small houses he owned and who filled his days with prayer and study in the local synagogue. The formative influence on the young Waksman was his mother, Fraida, who ran a small dry goods business. She was learned, especially for a woman of that period and place. She knew Yiddish literature, had enough knowledge of Hebrew to read scriptures, and could speak Ukrainian.

At the age of five, Waksman entered the local *cheder*, a Jewish religious school which stressed reading scripture and the intricacies of prayer. His mother worried about the limitations of such a parochial education, so she hired private tutors who instructed the ten-year-old boy in Hebrew and Russian as well as literature, history, arithmetic, and geography.

As a Jew in the waning days of the Russian Empire, Waksman had limited access to higher education. It was thus an easy decision for Waksman, especially after the death of his mother, to follow the example of a number of his relatives and immigrate to the United States. In 1910, he arrived in Metuchen, New Jersey, moving in with a cousin who had a small truck farm.



He soon enrolled at nearby Rutgers College, where he took accelerated course work and spent his fourth year on a research assignment assaying bacteria in culture samples from soil layers. It was while working on this project that Waksman found himself drawn to actinomycetes. These microorganisms became the focus of his masters' thesis at Rutgers and his doctorate, which he received from the University of California in Berkeley. He returned to Rutgers in 1918 as a Lecturer in Soil Microbiology at the college and Microbiologist at the Agricultural Station.

The later years

Streptomycin, of course, was the great success story of the Waksman screening protocols. There would be other antibiotics found, most notably neomycin, isolated by Hubert Lechevalier, which is still in use today as a topical antibacterial agent. But it was streptomycin that gained Waksman and his laboratory fame and fortune as well as controversy.

Waksman used part of the royalty income from antibiotics to establish the Institute of Microbiology to strengthen the study of the field at Rutgers. The official dedication of the Institute took place in 1954 with Waksman serving as director for its first four years. The new Institute had well-equipped laboratories and a fermentation pilot plant.

In 1952 Waksman received the Nobel Prize in Physiology or Medicine for "your ingenious, systematic and successful studies of the soil microbes that have led to the discovery of streptomycin." The Nobel Prize was one of many awards and plaudits that Waksman received in his later years. He died in 1973.

National Historic Chemical Landmark

The American Chemical Society designated the research of Selman Waksman and his students into the actinomycete antibiotics a National Historic Chemical Landmark on May 24, 2005. The plaque on the Cook Campus of Rutgers University commemorating the event reads:

Here, in Martin Hall, Selman A. Waksman and his students isolated antibiotics produced by actinomycetes, most notably streptomycin, the first effective pharmaceutical treatment for tuberculosis, cholera, and typhoid. They also isolated neomycin, used as a topical antibacterial agent. These discoveries emerged from Waksman's research program, which developed novel screening protocols for detecting antimicrobial agents in the soil. Waksman received a Nobel Prize in 1952 for "ingenious, systematic and successful studies of the soil microbes" that led to the discovery of streptomycin.

About the National Historic Chemical Landmarks Program

The American Chemical Society, the world's largest scientific society with more than 158,000 members, has designated landmarks in the history of chemistry for more than a decade. The process begins at the local level. Members identify milestones in their cities or regions, document their importance, and nominate them for landmark designation. An international committee of chemists, chemical engineers, museum curators, and historians evaluates each nomination. For more information, please call the Office of Communications at 202-872-6274 or 800-227-5558, e-mail us at nhclp@acs.org, or visit our web site: www.chemistry.org/landmarks.

A nonprofit organization, the American Chemical Society publishes scientific journals and databases, convenes major research conferences, and provides educational, science policy, and career programs in chemistry. Its main offices are in Washington, DC, and Columbus, Ohio.

Acknowledgments:

Written by Judah Ginsberg

Photo Credits: Rutgers University Archives

Photos on cover: (Clockwise from upper left) Martin Hall; Stamp issued by Gambia; Waksman's Nobel medals; Waksman with Boyd Woodruff; Waksman on the cover of Time, November 7, 1949; Waksman with Alexander Fleming.

In addition to consulting the standard reference works on Waksman, some of the important scientific papers on the development of antibiotics at Rutgers University, and the Waksman Papers at Rutgers, which are cited in the text, the author interviewed Drs. Boyd Woodruff, David Pramer, and Carl Schaffner. The author also wishes to thank Dr. Woodruff and Dr. Hubert A. Lechavelier for providing further insights in writing into the events described in the preceding pages. He also wishes to thank Dr. Douglas Eveleigh of Rutgers University for guiding him through the thickets of the history of the discovery of the actinomycete antibiotics. Needless to say, any remaining errors are his alone.

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