AEM Journals.ASM.org

Selman A. Waksman, Winner of the 1952 Nobel Prize for Physiology or Medicine

H. Boyd Woodruff

Soil Microbiology Associates, Watchung, New Jersey, USA

The history of the discovery and development of streptomycin is reviewed here from the personal standpoint of a member of Dr. Selman Waksman's antibiotic screening research team. The team approach of eight individuals illustrates how the gradual enhancement of the screening methodology was developed. I illustrate three study periods with key aspects in the development of streptomycin which led to a Nobel Prize being granted to Professor Waksman. One item not previously emphasized is the employment of a submerged culture technique for large-scale production of streptomycin, thus enabling rapid animal testing and human clinical trials with *Mycobacterium tuberculosis*. Another is that purified streptomycin was shown by Dr. Waksman to be distinctly different from the substances called natural products, which are no longer patentable in the United States; therefore, streptomycin was found to be patentable. A third item not previously emphasized is his emphasis on the screening of actinomycetes, including the newly named *Streptomyces* genus. All of these factors contributed to the success of streptomycin in the treatment of tuberculosis. In combination, their successes led to Dr. Waksman's department becoming a new pharmacological research area, specializing in drug discovery. These unique accomplishments all burnish the prior rationales used by the Karolinska Institute in granting Dr. Waksman alone the 1952 Nobel Prize for Physiology or Medicine.

At the end of 2012, the School of Environmental and Biological Sciences of Rutgers University held a major symposium to celebrate the 60th anniversary of Professor Selman A. Waksman's being awarded the Nobel Prize for Physiology or Medicine in 1952. Dr. Waksman's studies had led to the discovery of streptomycin, a new antibiotic. Streptomycin was the first effective cure for tuberculosis (TB). Its history, however, is a rather complicated story. It persistently presented problems for Dr. Waksman up to his death in 1973.

As an early research participant at Rutgers, in 1939 I studied under Dr. Waksman while working toward a Ph.D. degree (Fig. 1). Afterwards, I became employed at Merck & Co., Inc., where I conducted further microbial research with Dr. Waksman while he served as a consultant. Eventually, I received an assignment to record the history of Dr. Waksman's activities, culminating in this document.

The history was orally presented at the opening of the 2012 symposium. It also served to introduce several research specialists who planned to discuss various approaches to overcome the gradual loss of effectiveness of streptomycin over a period of 60 years. Streptomycin often required a 6-month treatment period to achieve a permanent cure of tuberculosis. That long time period resulted in the appearance of streptomycin-resistant *Mycobacterium tuberculosis* cells, caused by mutation. Then, especially in developing countries, due to the cost and inconvenience, many treatments were being shortened, leading to the requirement for repeated treatment and the release of even more streptomycin-resistant cells; thus, tuberculosis still remains a serious disease today, even though several additional drugs have been added to supplement the treatments. In Africa, recent mass treatments have resulted in less than 50% success. Fortunately, in the United States and other countries where TB-infected patients have been carefully managed, the problem is not yet as severe. Regardless, a solution must be found. Therefore, we were pleased to learn that the experts at the symposium would discuss approaches to overcome the problem.

ANTIBIOTIC TIME PERIODS

Streptomycin's history actually involves three separate time periods. The first goes back into the 1920s. During that long-ago period, the Rutgers Agriculture School's long-time soil microbiology professor, Robert Starkey, was serving as Dr. Waksman's Ph.D. student. Dr. Waksman and Robert Starkey together very actively studied microbes of the soil, with Starkey being first a student and later a companion teacher. Dr. Waksman, with the aid of numerous Ph.D. students, continued to establish soil microbiology as a discipline over the next 15 years, before his primary interest became antibiotics. Back in 1923, Waksman and Starkey, as professor and student, discovered that rather complex soil bacteria, the actinomycetes, when multiplying in soil were killing many common bacteria also growing there.

They stated that "Certain actinomycetes produce substances toxic to bacteria . . . around an actinomycete colony, upon a plate, a zone is found free from bacterial growth" (1). These findings were published and were available to all scientists, so one might expect the first discovery of an antibiotic, such as streptomycin, would have been reported shortly thereafter, that is, 90 years ago. The information obtained was clear in their published record. It seems that researchers active at that time who read the data should have realized that the bacteria killed in soils by soil actinomycetes could easily have been human pathogens growing there, being killed by an antibiotic, to our benefit. However, the idea that an active antibiotic might be present among the soil actinomycetes seems to have escaped the microbiologists of that time, including

Published ahead of print 25 October 2013

Address correspondence to H. Boyd Woodruff, boydwoodruff@optonline.net.

doi:10.1128/AEM.01143-13

The views expressed in this Commentary do not necessarily reflect the views of the journal or of ASM.

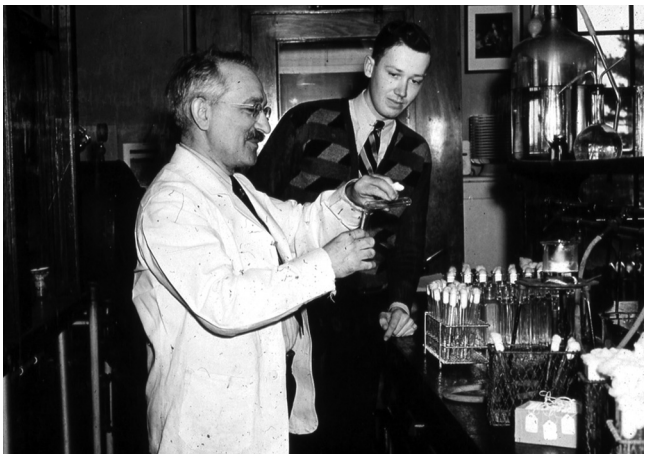

FIG 1 Professor Selman Waksman with graduate student H. Boyd Woodruff. Laboratory photograph during the studies leading to the discovery of actinomycin, 1940. Administration Building, School of Environmental and Biological Sciences (SEBS), Rutgers University. (Special Collections and University Archives, Rutgers University Libraries. With permission.)

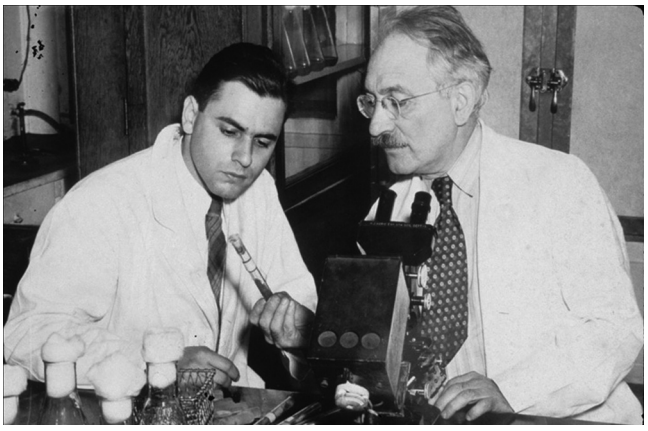

FIG 2 Professor Selman Waksman with graduate student Albert Schatz. Laboratory photograph during the studies leading to the discovery of streptomycin, 1944. Administration Building, SEBS, Rutgers University. (Special Collections and University Archives, Rutgers University Libraries. With permission.)

Dr. Waksman, and so that first, preantibiotic period lasted less than 1 year.

In 1937, Dr. Waksman suddenly realized that the actinomycete-bacterial fight to the death, observed much earlier with his student Starkey, needed to be investigated in further detail, but he wanted it done scientifically. He selected two of his best Ph.D. students to aid him. The first student, Jackson Foster, studied the battles taking place when mixtures of microbes were placed together on a laboratory bench. The second student, Imri Hutchings, covered the interactions that were occurring between various microbes while they were destroying plant residues. Their reports, plus Dr. Waksman's historical report, were published in 1937 (2–4).

The second antibiotic research period occurred thereafter, covering a 5-year period from 1939 to late 1943. Dr. Waksman, with his reawakened interest in antibiotics, had gathered eight researchers together to specialize in antibacterial studies, and as a new Ph.D. student in 1939, I was included. We eight were engaged in various research efforts dealing with antibiotics. We quickly discovered a few new ones: actinomycin, streptothricin, fumigacin, and clavacin. Unfortunately, all four were toxic to animals. In the final portion of that 5-year period, Albert Schatz, the most recent Ph.D. student joining our group to search for antibiotics, arrived and started his research under Dr. Waksman (Fig. 2). Then, he was drafted into the army. After a few months, he was released and was able to return and actively search for a useful antibiotic, again under the direction of Dr. Waksman. In his 11th consecutive soil plating, each of which required less than a week's time, including checking for the presence of an antibiotic, he isolated a *Streptomyces griseus* strain from the farm soil of the Rutgers Agriculture School. That strain produced an antibiotic (5). The culture differed little from Dr. Waksman's many prior *Actinomyces griseus* isolations made over his many years of research, but the presence of an antibiotic was new. Dr. Waksman and his student Schatz named it streptomycin. A sample was given by Dr. Waksman to the Mayo Clinic's expert researchers Drs. William Feldman and Corwin Hinshaw, who were specialists in tuberculosis studies, and after testing it, they reported that it was not toxic to various animals. It was the first Rutgers antibiotic obtained that was not toxic to animals. Therefore, Schatz's culture was a very significant discovery.

The third study period started almost immediately. In an unbelievably short period of time, there were many accomplishments. Dr. Waksman asked the specialists at the Mayo Clinic to use streptomycin in a new tuberculosis screening technique they had developed using guinea pigs. The guinea pigs responded typically when infected with an *M. tuberculosis* inoculum. It was assumed that would eventually be the case when humans were tested, but guinea pigs were responding first, very quickly. Streptomycin proved to be curative for infected guinea pigs, the first drug to do so (6). Dr. Waksman was asked to release larger amounts of streptomycin to the Mayo Clinic so that humans could be treated. He agreed to do so, with his student Schatz preparing the material. At the Mayo Clinic, the experts eventually found that streptomycin could overcome tuberculosis in humans.

INDUSTRIAL NEEDS

Merck and Co., Inc., a Rahway, NJ, pharmaceutical company for which Dr. Waksman was serving as a consultant, then entered the scene. Their own scientists, together with the Rutgers Ph.D. students and Dr. Waksman as their leader, quickly obtained the standard information required by the FDA, and as a result, the FDA approved the marketing of streptomycin as a cure for tuberculosis. Merck built a factory in Virginia to produce streptomycin, and it became marketed worldwide. All of this was accomplished in less than 10 years, and it led to Dr. Waksman being awarded the Nobel Prize for Physiology or Medicine in 1952 (7). This is a brief history of the events leading to Dr. Waksman receiving the Nobel Prize. However, it becomes more interesting when the research details are examined.

EXPANDED HISTORY

Dr. Douglas Eveleigh, of the School of Environmental and Biological Sciences at Rutgers, asked me to present this historical story in detail. As a member of Waksman's team of eight assigned to find a new useful antibiotic, it seemed appropriate that I do so. We also discussed the opportunity to fulfill a secondary objective, to gather details of Dr. Waksman's past research activities that would pro-

vide additional evidence justifying why he alone received that Nobel Prize. My initial feeling, however, was to decline that request. My age is 95 years, and we would have to discuss activities ranging over many years. Then I realized that I was the only known survivor of the eight Ph.D. candidates who had worked actively together with success under Dr. Waksman's leadership. I decided I had an obligation, and so I agreed to do so.

During Dr. A. Wallgren's Nobel Prize presentation speech in 1952, he stated, "Selman Waksman, the Caroline Medical Institute has awarded you this year's Nobel Prize for Physiology or Medicine for your ingenious, systematic and successful studies of soil microbes that led to the discovery of streptomycin." Based on my understanding of this statement, in Selman Waksman's case, it meant his Nobel Prize was based on two activities. First was his important background. He had completed 24 years of detailed early research on soil microorganisms, something new that others had only minimally tackled. Then, after that period, Dr. Waksman's research interests had shifted to antibiotics produced by actinomycetes. Student Albert Schatz, acting under his direction, found the culture that produced the new antibiotic streptomycin, and it was quickly established as the prime treatment for tuberculosis worldwide, as well as for many diseases caused by Gram-negative bacteria that were not previously treatable. These events provided the basis for Dr. Waksman receiving the Nobel Prize in 1952.

BACKGROUND MATERIAL

There is much background material available. In 1910, Selman Waksman emigrated from Ukraine (then part of Russia) to join family living in Metuchen, NJ. The next year, he enrolled as an undergraduate student at nearby Rutgers College. His professor, Dr. Jacob G. Lipman, soon discovered that he was a skillful researcher. As a student, Waksman completed the school's Bachelor of Science degree requirements within 3 years, so Dr. Lipman proposed that during his senior year he spend his time growing and researching a wide list of soil microbes. For Waksman, it proved to be an interesting year, with Dr. Lipman presenting his student's results in abstract form at the 17th Annual Meeting of the Society of American Bacteriologists under the title "Bacteria, Actinomycetes and Fungi in Soil," printed in the first volume of the *Journal of Bacteriology* (8).

Next, Dr. Lipman recommended that Selman Waksman achieve a Master's degree but this time his studies should be based on actinomycetes only. Actinomycetes are rather slow-growing filamentous soil bacteria, and at that time they were seldom studied. Selman Waksman spent his entire time during his Master's year studying them. In fact, they became his favorite organisms for future studies, especially *Actinomyces griseus*. He took several actinomycetes with him for studies in biochemistry at the University of California, Berkeley, and he received a Ph.D. degree there. Then, he returned to the Rutgers' Agricultural School as an employee.

As I mentioned above, one of Dr. Waksman's favorite cultures was *Actinomyces griseus*. He had spent much time studying it. Then, 28 years later, under a more modern name, *Streptomyces griseus*, it was reisolated by his student Albert Schatz. Interestingly, the new genus name, *Streptomyces*, which was applied to his student Schatz's isolate, actually had been created by Dr. Waksman himself when working together with Dr. Arthur T. Henrici during a former realignment of the official names of the actinomycetes.

DR. WAKSMAN'S SHIFT TO ANTIBIOTICS

In 1939, four years before the discovery of streptomycin, I arrived at Dr. Waksman's office in the Rutgers Agriculture School as a new Ph.D. student. About a month after my arrival, Dr. Waksman excitedly came rushing into my laboratory and cried out "Woodruff, Woodruff, drop everything. My former student René Dubos has discovered a way to find antibacterial agents produced by soil microorganisms. And he found an antibiotic; I am impressed. We must discover a better one."

His former student René Dubos had added living pathogenic bacteria repeatedly to soil. He hoped that some minor microbe in the soil would be capable of killing the pathogen and would use the dead cells as a nutrient and start to multiply to the point that he could isolate it. He was successful. He isolated a microbe that produced an antibiotic, and he named the antibiotic tyrothricin. It cured localized staphylococcal infections in humans when applied to the infected site. Dr. Dubos had just published these data (9), and Dr. Waksman was fascinated by them.

Dr. Waksman rather excitedly directed me to repeat the Dubos procedure but stated that I must make significant changes. First, I must use a Gram-negative pathogen as the target to be destroyed in my soil pot, not the Gram-positive microbe that Dr. Dubos had used. Waksman knew that Gram-negative organisms were not being killed by the newly developed penicillin, whereas Dr. Dubos's Gram-positive organism was, so finding drugs to treat Gram-negative pathogens had to receive top priority. *Escherichia coli* was chosen to be our Gram-negative target cell, based on undergraduate studies showing that *E. coli* cells can easily be counted due to a metallic sheen they develop when they are grown in a special culture medium (10). With it, the number of *E. coli* cells still surviving in soil pots could be determined after millions of the bacteria had been added a week previously. In fact, the number of living *E. coli* cells in the soil pots did decrease, slowly at first and then faster and faster, and finally, after 2 months of weekly *E. coli* additions, a week after the last addition was made, no living *E. coli* cells could be found in the soil pot. All seemed to have been killed, probably by an antibiotic. So, the remaining soil was plated, and surprisingly, about half of the cultures obtained were able to inhibit the growth of *E. coli*. Microbes inhibiting *E. coli* growth had increased in the soil pot. One such culture, whose antibiotic could be extracted by a solvent, was selected. Dr. Waksman gave some extract to Dr. Max Tishler, leader of chemistry at Merck, and within a week Dr. Tishler had obtained crystals. Dr. Waksman decided to name them actinomycin (11, 12). We believed our actinomycin was the most active antibiotic ever discovered, but it soon proved to be one of the most toxic ones.

NEW ANTIBIOTICS

Dr. Waksman was greatly excited by the discovery of actinomycin. He started rearranging his department to specialize solely in antibiotics. He added a new program, headed by my companion Ph.D. student, Elizabeth Horning, to search for antibiotics produced by molds. Elizabeth was a very efficient student. She had been previously employed and had requested half-time release to pursue a Ph.D. She attended classes at Rutgers, but most experimental work was continued at her commercial laboratory a few miles away. Amazingly, without the benefit of student discussions, she made rapid progress. She modified the screening approach to direct soil plating, with subsequent analysis of the copious isolates for their antagonistic activity. Two new mold antibiotics were

found; one was named fumigacin and the other clavacin (13). But these two, like our actinomycin, proved to be highly toxic. She also isolated 244 actinomycetes, 31 of which were determined to have antagonistic activity, although broader screening was not accomplished. By that time, with Dr. Waksman's aid, I had purified a newly obtained and different actinomycete antibiotic. We named it streptothricin (14). It was less toxic, proving it was possible for one to discover less-toxic antibiotics, but even streptothricin was not sufficiently suitable for wide-scale human use, as proved by a brief trial with humans as targets, so the search for safer ones continued.

DR. WAKSMAN AS A RESEARCH LEADER

Immediately it was learned why Dr. Waksman had been so effective as a past leader in science. As he had done several times with other students, he joined me, working at our laboratory bench. So, for a year, I became his laboratory assistant, serving him for about half of each day. It turned out to be a wonderful learning period for me, and it lasted about a year. Then, after two more years of personal research, when I was nearing the end of my Ph.D. studies, Dr. Waksman sent me to Merck & Co., 6 months before my graduation date, with the assignment to aid the Merck microbiologists in establishing, on an industrial scale, a new type of submerged culture for production of commercial amounts of penicillin. The new submerged culture procedure had been strongly recommended to the Merck workers by Dr. Waksman, because he had used it successfully. It would be my responsibility to make certain it was adopted at Merck for penicillin production. Submerged culture was a new technique. It involved very large aerated tanks, able to produce a desired product from top to bottom of the large tank, with great volumes achieved, in contrast to the usual surface cultures of actinomycetes, where from hundreds up to thousands of trays were needed to achieve a relatively small volume. The new leader of Merck's Microbiology Department was Dr. Waksman's prior student Jackson Foster, who had studied these microbes successfully. Dr. Foster immediately adopted the new industrial-scale submerged-culture procedure for the production of penicillin. The new procedure had been brought home by Dr. Starkey, who had spent a sabbatical with Dr. Kluyver in Delft, the Netherlands, and Dr. Waksman adopted it immediately, using shaking machines as a means of producing citric acid in large quantities, working with another Ph.D. student, Edward Karow.

NATIONAL ACADEMY OF SCIENCES

During the time that I was still his student, Dr. Waksman received the honor of being elected to membership in the National Academy of Sciences. His election was based largely on his early basic research on soil microbes, that is, the same portion of his work that later influenced the Nobel Prize Committee, plus his search for antibiotics. Those who voted him into membership in the National Academy were the leading scientists of the world, so I felt that the honor he had received was truly very great.

EXPANDED ANTIBIOTIC STUDIES

Ph.D. student Albert Schatz had been placed in my prior student position in Dr. Waksman's solely university-financed Ph.D. program (as I had gone on to research at Merck Research Laboratories). All others were financed by outside interests. He was deeply interested in discovering antibiotics produced by actinomycetes. Dr. Waksman asked him to continue the *E. coli* Gram-negative

FIG 3 The Waksman antibiotic team. Department reunion, Society of American Bacteriologists Annual Meeting, Philadelphia, PA, 1947. Standing (left to right): David Hendlin (fosfomycin at Merck), Albert Schatz (streptomycin), H. Boyd Woodruff (actinomycin and streptothricin), Elizabeth Horning (clavacin and fumigacin), and Ed Karow (development of submerged fermentation). Seated (left to right): Christine Reilly (streptomycin development), Mrs. Deborah Waksman, Dr. Wayne Umbreit (visiting researcher), Professor Selman Waksman, and Professor Robert Starkey. Front row (left to right): D. Montgomery Reynolds (grisein) and Harry Katznelson (rhizosphere studies). (Department of Microbiology Collections, Rutgers University. With permission.)

approach. However, as previously stated, Schatz's student days were interrupted when he was drafted into the military, but only briefly. Then, after returning to Rutgers, he felt he needed to increase the number of antibiotics studied. Nontoxic ones seemed to be very rare, so he felt he must change to an easy screening approach from the previously used slow, 2-month scientific approach. Elizabeth Horning had done so successfully with molds. So, he changed to a well-known simple plating technique to isolate many new soil actinomycete cultures. Platings were performed on washed *E. coli*, *M. tuberculosis* (*hominis*), and *Sarcina lutea* cells. Since the indicator cells were rarely completely clear, cells were taken from all growth levels for further study, and so many checks were made for the presence of antibiotics. Thus, his student Schatz increased the number of cultures evaluated many times over what were evaluated in the prior 2-month tests used, when that soil had been tested, *E. coli* disappeared completely, and actinomycin had been discovered. His simple approach proved successful (15). Based on the Mayo Clinic's evaluation, he had obtained streptomycin, a new antibiotic which was safe for animal treatments, and it proved effective in curing tuberculosis (Fig. 3 and 4).

PATENTS

Dr. Waksman was worried that his student Schatz's screening approach would lead to a failure to receive a patent for streptomycin because it was routine. Natural products had been banned from receiving American patents by then, so he feared streptomycin would fail to yield one. The Merck lawyers felt they would be successful. They had succeeded in patenting Dr. Waksman's actinomycin and streptothricin antibiotics. However, to accomplish that, Dr. Waksman's aid had been needed. He studied and then reported his results to the patent specialists. He made it evident that crystalline antibiotics and other high-potency preparations are very different from the natural products that exist in soils. He argued that purified antibiotics were no longer natural products

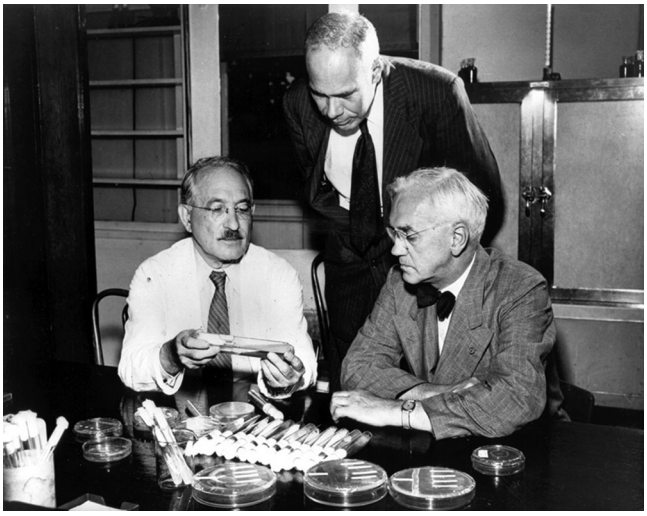

FIG 4 (Left to right) Professor Waksman with Randolph Major (Research Director, Merck and Co.) and Alexander Fleming (Nobel Laureate, penicillin), discussing the cross-streak antibiotic screening technique. Waksman laboratory, Administration Building, SEBS, Rutgers University, 1940s. (Special Collections and University Archives, Rutgers University Libraries. With permission.)

and, therefore, they should be patentable, and they eventually were judged to be so. The Merck lawyers planned to again use Waksman's arguments to obtain a streptomycin patent, and they were successful.

Years later, Dr. Waksman was fully retired. He still had an office in the newly built Microbiology Building on Rutgers' Busch campus. Its construction, at Dr. Waksman's request, had been funded by streptomycin patent royalties. He called me often on the phone at Merck, always saying approximately the same thing: "Come visit me, right away; I have several new ideas and I would like to discuss them with you." So, I would drive down, but I often found him forgetful, due to his advanced age, often failing to recall the reason for asking me to come. But we almost always ended up discussing various aspects of his past scientific activities. On one occasion, he told me he had enjoyed working at the laboratory bench with me for a year because our target, the killing of Gram-negative *E. coli* cells, was research based. However, after his student Schatz had replaced that approach with his routine soil platings, Dr. Waksman said he felt it was no longer a true research project, just screening, so he could not bring himself to work with Schatz at his basement laboratory bench to help broaden his studies. But, in fact, Waksman had become greatly concerned. He felt his failure to work with Schatz in his basement laboratory several years in the past had led to some complications that had developed between them.

COMPLICATIONS

The complications between Dr. Waksman and Dr. Schatz, after the latter had graduated, became truly serious. The distribution of royalties on the sale of streptomycin had not been clearly defined and became altered as time went by. Eighty percent of the funds were set aside for the construction of a new microbiological research program at Rutgers' Busch campus, which had become the center for the university's scientific programs. Dr. Waksman accepted rights for the 20% royalty remainder, primarily to expand research on streptomycin beyond the scope of Rutgers University. He felt strongly that it was necessary to do so for any patented discovery made in a university. He spent the funds on purchases of streptomycin, and he supported studies on it by other universities and other established research programs. Later, a change in royalty distribution was introduced, such that Dr. Waksman should receive some royalty funds as a salary to add to his university income, because it was taking so much of his working time.

Dr. Waksman was absolutely shocked when a legal suit was filed by Dr. Schatz against him and the university, especially after Dr. Schatz, as a postdoctoral scientist, had obtained several research positions based on Dr. Waksman's recommendations. The university management had adopted a procedure by a vote, accepted by Dr. Waksman, that the royalty funds should be directed to the university laboratory where the discovery had been achieved, that is, the Soil Microbiology Department of the Agricultural College. The legal suit thereafter became a severe concern for Dr. Waksman.

The case, however, was actually settled before going to court. Dr. Schatz accepted a proposal put forward by Dr. Waksman. Although not preapproved officially by the legal staff, Dr. Waksman decided that if he were to receive royalties as salary, similar gifts should be passed to students and laboratory employees who had been involved with streptomycin. He proposed that 10% of the royalties should be passed to them, 26 persons in all, the majority as lump sums and other portions as percentages for the remaining royalty period, with Dr. Schatz, as discoverer of the streptomycin-producing culture, receiving the largest fraction. Dr. Schatz accepted the proposal. This settlement restored somewhat the relationship between Dr. Schatz and Rutgers University. Several important awards, including the Rutgers Medal, were given to him by Rutgers University's top management. Also, some lectures by Dr. Schatz were presented in Rutgers facilities during the 50th anniversary of the discovery of streptomycin. Later, Rutgers Agriculture School students insisted that a plaque showing that Albert Schatz was truly a codiscoverer of streptomycin must be placed in the building where streptomycin had been discovered, and this was done.

GENERAL SCIENTIFIC ACTIVITIES

At the beginning of this commentary, referring to streptomycin, I stated that its history is rather complicated and that it persistently presented problems for Dr. Waksman. I believe the primary reason for that is now clear. However, I do believe we should have a paragraph or two to demonstrate that Dr. Waksman's general scientific activities were important and were widespread. I had attended his undergraduate soil microbiology course. Dr. Robert Starkey, the regular professor, was on sabbatical leave in Holland, so that year Dr. Waksman was teaching both the graduate students and the undergraduate seniors. He had selected a graduate-level lecture with which to open the undergraduate class. It had a major effect on me. I was amazed at the possibilities offered by soil microbiology, and I immediately decided I would become a soil microbiologist. Professor Waksman reported how his tiny microorganisms had achieved major breakthroughs, certainly far more frequently than discoveries I had observed in chemistry, my prior interest. Furthermore, Dr. Waksman was creative as a teacher. As an immigrant, he was so sold on the U.S. form of government, in contrast to his experiences in Russia, that he required all of his graduate students, foreign and local, to visit Philadelphia with him

and evaluate this country's formation and its constitution. Each summer, he also insisted that a day must be spent by his Ph.D. students and friends at the New Jersey seashore or, in autumn, at parks in the nearby Pocono Mountains. He insisted on preparing the hot dogs on those occasions.

EVOLUTION OF SAB TO ASM AND OF *APPLIED MICROBIOLOGY* TO *APPLIED AND ENVIRONMENTAL MICROBIOLOGY*

Dr. Waksman had a great interest in the Society of American Bacteriologists (SAB), now the American Society for Microbiology (ASM). He was elected President of SAB during a complex period. It was the beginning of World War II, when for the first time an SAB Annual Meeting was cancelled. However, in addition to his general research responsibilities, he was tremendously busy. He was greatly concerned that the SAB was on the verge of breaking apart. Because practical studies were only occasionally accepted by its journal, the concern became greater and greater as time went by. Eventually, the *Journal of Bacteriology* publisher, Williams and Wilkins, agreed to finance an applied journal. Committees were established, and the new journal *Applied Microbiology* was established, initially with bimonthly publication. By the end of its first decade, during which I was Editor in Chief, it had proven to be a profitable journal. New editors transitioned it to a monthly publication, then semimonthly, and the name was eventually changed to *Applied and Environmental Microbiology*. *Applied and Environmental Microbiology* eventually became one of the most successful journals published by ASM, demonstrating that a very large number of individuals had become interested in applied and environmental microbiological problems.

CONCLUDING COMMENTS

Again, let us return to the Nobel Prize and my assigned responsibilities. First, I was asked to edit a new book covering Dr. Waksman's full scientific lifetime activities (16). During his scientific lifetime, Dr. Waksman published 447 articles, a very large number. His new book, 391 pages long, was divided into 11 topics. Ten were for 10 different areas he had studied during the first half of his research years on soil microbes, thereby fulfilling initial support for his being awarded the Nobel Prize. The 11th topic was antibiotics, which covered the latter half of his productive life. Many of the first 10 topics clearly fit the ingenious, systematic, and successful studies of soil microbes, the Nobel objectives mentioned by Dr. Wallgren. I calculated that 127 of his early published papers met those requirements. The 11th topic, the discovery of antibiotics, encompassed 198 additional Waksman publications, including the discovery of streptomycin. All were determined to be of value as part of the Nobel award's basic efforts, thus leading to more than 300 publications supporting his being awarded the Nobel Prize.

Second, after Dr. Waksman's death, the Soil Science Department at Rutgers requested an official obituary, to be published in a major encyclopedia. The following is a small quotation taken from the rather long obituary:

> Selman Waksman was a prolific writer, publishing papers in a wide range of scientific journals, in several languages. He was author or coauthor of 28 books. His "Principles of Soil Microbiology," an 897-page volume, the first edition published in 1927, for years became the standard text book of his field. He guided 78 students to graduate degrees. He was an inspiring lecturer. His presentations included stories of his relationships with leaders of his field and were avidly followed by his students and audiences. He was beloved by his students, recent ones spoke of him as the "The Old Maestro." Waksman's name is generally included with Winogradsky, Omeliansky, Beijerinck and the Americans Lipman and Thom in lists of the pioneers of soil microbiology.

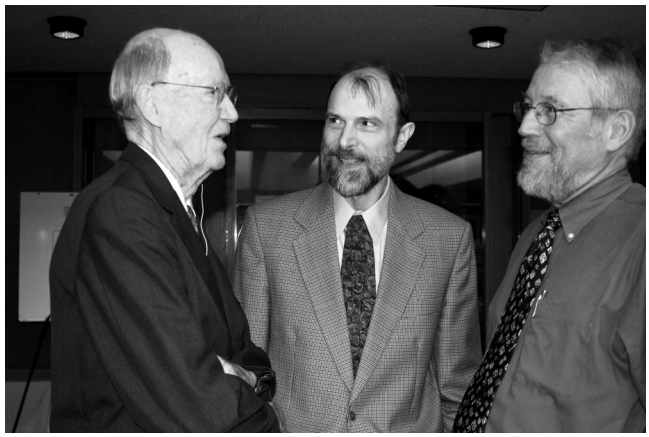

FIG 5 (Left to right) H. Boyd Woodruff in discussion with Joachim Messing (Director, The Waksman Institute) and Robert Goodman (Dean, SEBS) at the opening of the Selman Waksman Room, Library of Science and Medicine, Rutgers University, and celebration of H. B. Woodruff's 90th birthday, July 2007. (Photograph courtesy of Douglas E. Eveleigh. With permission.)

Let me summarize the new points which I believe added to the significance of that Nobel Prize. They are 4-fold and have been referred to already. First, Dr. Waksman passed the new submerged culture approach, originally from Holland, on to Merck for use in the production of penicillin and streptomycin, and he used it himself to produce citric acid. Second, he was responsible for the Merck lawyers successfully obtaining patents for Waksman's antibiotics, actinomycin, streptothricin, and, later, streptomycin, by showing that crystalline and highly concentrated products differed appreciably from the natural soil products, thereby opening the door for patents on hundreds of new discoveries by others. Third, he had created the new genus name *Streptomyces* and, with his friend Arthur T. Henrici, realigned the actinomycete taxonomy. Finally, he had led his department in finding various new drugs, with the methods used being copied later by dozens of commercial organizations. These supplemental items justified his being the sole awardee of that 1952 Nobel Prize.

I believe my assignment today, to describe the sequence of events leading to Dr. Waksman's attainment of a Nobel Prize 60 years ago, has been fulfilled. I now come to the end of my history (Fig. 5). It was intensely interesting to have been a participant in these life-long happenings, leading to medical discoveries, and for that I am greatly indebted to my 40-year association with Dr. Waksman.

After my oral history was presented in December 2012, the remainder of the 60th Anniversary Lectures were presented, related in part to finding new streptomycin equivalents as replacements for streptomycin itself or discussing alternate approaches to overcome the disease. The fact that experts are still actively searching for a new useful drug to be used to control tuberculosis is

consoling, but the slow progress is worrisome. Indeed, as reported, only about 50% success in TB control is being achieved in developing countries at present, even with the addition of new drugs. Also, there is concern regarding the possible rapid spread of streptomycin-resistant TB disease in the immediate future, with no remaining drug replacements available.

ADDENDUM

An item was published in The New York Times Business Section on 1 January 2013, shortly after our 2012 celebration was held. It was entitled "F.D.A. Approves Drug for Resistant Tuberculosis." Therefore, the situation may not be as dire as I have feared (17).

ACKNOWLEDGMENTS

I have greatly appreciated the aid of Douglas E. Eveleigh, School of Environmental and Biological Sciences, Rutgers University, in converting an oral lecture into a printed commentary. He has confirmed the validity of statements made, aided in article condensation, and, especially important, obtained acceptance for publication in *Applied and Environmental Microbiology*, a special honor for me, having served 10 years as its organizing editor. Dr. Eveleigh was especially helpful in organizing the publication, being skilled in historical observations and well trained by contact with widespread historical institutions, including the Natural History Museum and the Science Museum, London. His special fascination has been with microbial abnormalities occurring in New Jersey, dating back to Rutgers University's pre-United States years.

REFERENCES

1. **Waksman SA, Starkey RL.** 1923. Partial sterilization of soil, microbiological activities and soil fertility. Soil Sci. **16:**343–358.
2. **Waksman SA.** 1937. Associative and antagonistic effects of microorganisms. I. Historical review of antagonistic relationships. Soil Sci. **43:**51–68.
3. **Waksman SA, Foster JW.** 1937. Associative and antagonistic effects of microorganisms. II. Antagonistic effects of microorganisms grown on artificial substrates. Soil Sci. **43:**69–76.
4. **Waksman SA, Hutchings IJ.** 1937. Associative and antagonistic effects of microorganisms. III. Associative and antagonistic relationships in the decomposition of plant residues. Soil Sci. **43:**77–92.
5. **Schatz A, Bugie E, Waksman SA.** 1944. Streptomycin, a substance exhibiting antibiotic activity against Gram positive and Gram negative bacteria. Proc. Soc. Exp. Biol. Med. **55:**66–69.
6. **Feldman WH, Hinshaw HC.** 1944. Effects of streptomycin on experimental tuberculosis in guinea pigs. Proc. Staff Meet. Mayo Clin. **19:**593–599.
7. **Waksman SA.** 1968. Streptomycin: background, isolation, properties, and utilization—Nobel lecture, December 12, 1952, p 287–305. *In* Woodruff HB (ed), Scientific contributions of Selman A. Waksman. Rutgers University Press, New Brunswick, NJ.
8. **Waksman SA.** 1916. Society of American Bacteriologists: abstracts of papers. Bacteria, actinomycetes and fungi in soil, p 101. J. Bacteriol. **1:**81.
9. **Dubos R.** 1939. Bactericidal effect of an extract of a soil bacillus on Gram-positive cocci. Proc. Soc. Exp. Biol. Med. **40:**311–312.
10. **Wikipedia contributors.** 2013. Eosin methylene blue, *on* Wikipedia, the Free Encyclopedia. http://en.wikipedia.org/wiki/Eosin_methylene_blue. Accessed 17 July 2013.
11. **Waksman SA, Woodruff HB.** 1941. *Actinomyces antibioticus*, a new soil organism antagonistic to pathogenic and non-pathogenic bacteria. J. Bacteriol. **42:**231–249.
12. **Waksman SA, Tishler M.** 1942. The chemical nature of actinomycin, an antimicrobial substance produced by *Actinomyces antibioticus*. J. Biol. Chem. **142:**277–286.
13. **Waksman SA, Horning ES, Spencer EI.** 1942. Two antagonistic fungi, *Aspergillus fumigatus* and *Aspergillus clavatus*, and their antibiotic substances. Science **96:**202–203.
14. **Waksman SA, Woodruff HB.** 1942. Streptothricin, a new selective bacteriostatic and bactericidal agent, particularly active against Gram-negative bacteria. Proc. Soc. Exp. Biol. Med. **49:**207–210.
15. **Waksman SA, Schatz A.** 1945. Streptomycin. J. Am. Pharm. Assoc. **6:**308–321.
16. **Woodruff HB (ed).** 1968. Scientific contributions of Selman A. Waksman. Rutgers University Press, New Brunswick, NJ.
17. **New York Times.** 1 January 2013. F.D.A. approves drug for resistant tuberculosis. New York Times, New York, NY.