

Streptomycin — arrogance and anger

Steve Ainsworth tells the story of the discovery of streptomycin and the controversy that followed as a result of credit and royalty disagreements

Build a better mousetrap and, according to Ralph Waldo Emerson, the world will make a beaten path to your door. That piece of 19th century wisdom was never better illustrated than 60 years ago this month, when, on 22 February 1946, another American went public to announce his discovery of a remarkable new mousetrap. The man was Selman Abraham Waksman, his mousetrap streptomycin and tuberculosis the vermin he set it to catch.

Penicillin was the wonder drug of the age. But what to do for an encore? For Alexander Fleming, the discovery of penicillin meant a knighthood, a Nobel prize and enduring fame. After that 1946 announcement, history would accord Selman Waksman similar iconic status. Not only had Waksman discovered streptomycin, according to the history books, he had also come up with a brand new word to describe it — “antibiotic”.

Yet popular history is often inaccurate or incomplete. Every schoolchild learns that Alexander Fleming discovered penicillin. Only professionals now recall that it was Howard Florey and Ernst Chain who did the hard work. Fewer still are aware that in 1924, four years before Fleming’s famous observation, two French scientists, André Gratia and Sarah Dath of the Pasteur Institute, published a paper on penicillium, which they had found was suppressing bacteria growth on a Petri dish. Fleming, however, was a far better self-publicist.

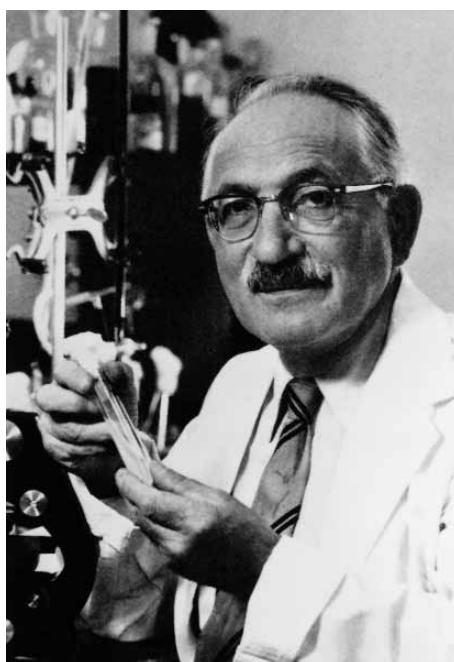
Controversy

The story of the genesis of streptomycin also features its share of controversy. Following the emergence of penicillin it was obvious that both fame and wealth would fall to whoever was able to find a second useful bacteria-destroying mould.

The development of penicillin at Oxford had been a combination of science and serendipity, a kitchen sink affair operating on a shoestring budget. With fortunes to be made, the American search for a second super drug would involve major investments in both time and money.

Dr Selman Waksman, a Russian immigrant to the US, was a world expert on soil-borne fungi and micro-organisms. Waksman worked at Rutgers University, New Jersey. There he, and up to 50 of his students, funded by Merck, systematically set out to find an organism which would be of use in treating tuberculosis. They investigated over 10,000 potential cultures.

In the autumn of 1943, one of Waksman’s team came across a mould, *Streptomyces griseus*,



A portrait of Selman Waksman, who won the Nobel prize for medicine in 1953 for the discovery of streptomycin

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taken from a chicken; from it he would develop streptomycin.

Just over a year later, on 20 November 1944, doctors at the Mayo Clinic administered streptomycin to a patient for the first time. The young woman had advanced pulmonary tuberculosis. Almost miraculously she recovered. Over the next decade, deaths from tuberculosis in the US and Europe would fall dramatically.

Waksman’s claim to fame was assured, so much so that in 1949 his face appeared on the cover of *Time* magazine. But not everyone would remain content for Waksman to hog the limelight. Not the least of them was the student working in Waksman’s team who had been the one actually to find and develop streptomycin. That individual was a young man of Russian and English descent, 23-year-old Albert Schatz. Studying for his PhD under Waksman, Schatz had been working furiously for three months before the breakthrough came. According to Schatz: “I generally began my work between five and six in the morning and continued until midnight, or even later. I was isolating and testing everything I could find.”

Though Schatz’s name had appeared first on the original published paper he eventually came to feel he had a right to share not only the academic kudos, but also the public fame and the cash which came with the discovery. Matters would take a distinctly nasty turn.

At the outset, Schatz showed no hint of a mercenary streak. Indeed, quite the contrary. In 1946, at Waksman’s request, Schatz had

signed over his royalty rights from the streptomycin patent to the Rutgers Research and Endowment Foundation. According to Schatz, this was on the understanding that neither Waksman nor the Foundation would ever directly profit from the discovery.

Schatz himself was content to make no money from streptomycin; he even returned cheques sent to him by Waksman, saying in correspondence that he would not know what to do with the windfall. Three years later, however, Schatz learnt that, contrary to his earlier assurances, Waksman had a personal agreement with the Rutgers Foundation to receive 20 per cent of all streptomycin royalties, a share which by then had amounted to \$350,000.

A furious Schatz sued. The huge negative publicity was deeply embarrassing to both Waksman and Rutgers. In December 1950, the case was settled out of court. The president of Rutgers issued a statement explaining that all parties recognised that Schatz was the co-discoverer of streptomycin. Under the agreement, Schatz was to receive a lump sum of \$120,000 for the foreign patent rights and 3 per cent of the royalties paid to the foundation, although 10 per cent was still going to Waksman and another 7 per cent split among all who had participated in the early work leading to the development of streptomycin.

Nobel prize

Despite the recognition of Schatz’s work, it was still Selman Waksman alone who, in 1952, was awarded the Nobel prize for medicine. Perhaps unsurprisingly, Waksman is reported to have made no mention of Schatz in his acceptance speech, nor did Schatz get a mention by name in Waksman’s 1958 autobiography, ‘My life with the microbes’.

Despite there being some problematic side effects still to overcome, streptomycin had nevertheless exceeded expectations. Not only was it the first effective treatment for tuberculosis, it was also effective against several other diseases such as typhoid, cholera and the bubonic plague.

Waksman died in 1973 at the age of 85. A legend in his lifetime, he had co-authored 500 scientific papers and written or edited some 28 books.

Schatz died in Philadelphia in January 2005 at the age of 84. As a result of his legal action he had effectively been labelled a troublemaker and had been blackballed by American academia; he never worked in a first-rate microbiology lab in the US again. In the early 1960s, unable to find work, he moved to South America where he worked as a professor at the University of Chile.

During his subsequent career, Schatz published three textbooks and more than 700 articles. In time he received a multitude of

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awards and medals from universities and societies throughout the world. He was awarded honorary degrees from Brazil, Peru, Chile and the Dominican Republic. In 1994, having long outlived Waksman, he even received the Rutgers University Medal, the university's highest honour.

Yet, despite his "rehabilitation", Schatz remained bitter to the end of his life, believing that Waksman consistently claimed more than his due. According to Schatz's recollection late in life: "The Mayo Clinic suggested that Waksman look for an antibiotic against tuberculosis, for which there was then no effective antibiotic treatment. Dr Waksman was disinclined to take on that project because he was afraid of tuberculosis. This disease had, by then, killed about a billion people in the last two centuries. That was more deaths than were caused by all other infectious diseases combined. However, I persuaded Dr Waksman to let me do the TB project. He agreed, but, because I would be working with a virulent human strain of the tubercle bacillus, he transferred me from the laboratory adjacent to his office on the third floor of the administration building, to the basement laboratory. He told me never to bring a culture of the tubercle bacillus to the third floor. And, he never visited the basement laboratory."

Justifiable anger from Schatz? Perhaps. Arrogance from Waksman? Probably.

But not according to Waksman. In 1950 he wrote: "... we developed all the methods for its isolation and had the name already available so that it was merely a question of screening a certain number of forms before we had the right organism. . . . It just happened that Schatz was concerned with some of the early isolations and tests, but . . . Miss Elizabeth Bugie and Miss H. Christine Reilly have made as important contributions, if not more so, in the discovery and development of streptomycin than Schatz has done."

Schatz could hardly say that he was denied academic credit. The original paper published in 1944 — titled "Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria" is unambiguously credited to A. Schatz, E. Bugie and S. A. Waksman.

Breaking point

Possibly the international acclaim, which the publicity-hungry Waksman willingly shared with no one, pushed Schatz to breaking point. But the real trigger for legal action seems to have been money, specifically his belated discovery that Waksman was now in receipt of a large income, despite his alleged earlier assurances that streptomycin would benefit the world, not enrich those individuals who had developed it.

Waksman and Rutgers' research funding agreement with Merck went back to 1939 and would have given Merck exclusive rights to streptomycin. By 1945, Waksman realised that streptomycin would become an important commercial product and became unhappy with the agreement with Merck.

Waksman even wondered whether Merck was large enough to be able to meet the potential demand for streptomycin; he also believed that prices could be reduced if several companies could manufacture the drug. As a result of these second thoughts, Waksman approached Merck requesting the abrogation of the 1939 agreement. Surprisingly, Merck agreed to the request, provided that a new agreement could be reached.

With commendable generosity, Merck assigned the streptomycin patent rights to Rutgers in exchange for a non-exclusive licence for its production. Rutgers soon



Albert Schatz in the laboratory, 1945: was he wrongly denied the glory and profit enjoyed by Selman Waksman?

reached licensing agreements with other drug companies. Meanwhile, to compensate the company for money spent in the development of streptomycin, Merck was granted a rebate on the royalties it had already paid.

Attacking a wide spectrum of diseases, not at least tuberculosis, streptomycin almost immediately began generating large profits; the royalties began pouring into Rutgers.

From the outset of its 1939 agreement with Merck, the Rutgers Foundation had been handing over around half its royalties from Merck to Selman Waksman personally. When Merck turned over the streptomycin patents to Rutgers in 1946, the organisation was re-established as the Rutgers Research and Endowment Foundation. At that time it became clear that the royalties were about to become a large amount of money and Waksman agreed to have his share of them reduced to a fifth. Four years later, as a result of Schatz's legal action, Waksman's share was again reduced, this time to 10 per cent — half of which he later voluntarily used to establish a new Foundation for Microbiology at Rutgers.

As for that Nobel prize, was Schatz really snubbed? In fact Waksman did mention Schatz in his 1952 Nobel lecture — but only

as one name in the middle of a list of two dozen colleagues formally thanked for their contribution.

By contrast, the Nobel Committee was not so sparing in its reference to Schatz. Professor A. Wallgren of the Royal Caroline Institute gave the presentation speech; in it he carefully spelt out that "Dr Waksman directed this work and distributed the various lines of research among his young assistants. One of these was Albert Schatz, who had previously worked with Dr Waksman for two months and in June 1943 returned to the laboratory. Dr Waksman gave him the task of isolating new species of actinomyces. After a few months he isolated two strains of actinomyces which were shown to be identical with *Streptomyces griseus*, discovered by Dr Waksman in 1915."

The Nobel Committee was well aware of the controversy surrounding the discovery of streptomycin, and it even recalled that Fleming, Chain and Florey had shared the 1945 prize.

In his speech, Professor Wallgren emphasised the differences: "In contrast to the discovery of penicillin by Professor Fleming, which was largely due to a matter of chance, the isolation of streptomycin has been the result of a long-term, systematic and assiduous research by a large group of workers. The initiator and leader of this group was Dr Waksman."

The 1952 Nobel prize for medicine was awarded, not for the discovery of streptomycin per se but for Waksman's "ingenious, systematic and successful studies of the soil microbes that have led to the discovery of streptomycin". And, before he finished, Professor Wallgren went on to praise Waksman for his other claim to fame: his introduction of the new word "antibiotic".

Sixty years on from the announcement of streptomycin's discovery, it is possible to be objective. Credit is often allocated unfairly; arguably it was Chain and Florey alone who deserved the Nobel prize, yet it is Fleming whose name endures.

Schatz was at least as deserving as Fleming. Yet if he had been honest with himself he must have realised that he, too, had been lucky; any one of Waksman's students could have been given the task Schatz was allocated — moreover it was a task devised by Waksman after 30 years of systematic study.

Today Waksman's name alone lives on, while Schatz, like Chain and Florey, is destined to be forgotten. Yet one question remains. Was Waksman completely honest? Though some elements of this story may be debatable, one fact is indisputable.

Waksman's continuing fame rests not only on the discovery of streptomycin but also on his invention of the word "antibiotic". Those who consult the Oxford English Dictionary, however, will see that Waksman was certainly not the man who coined that 19th century word. But, Selman Waksman was clearly not a man to contradict those who would grant him even greater glory than his due.

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