EXPERIMENT ELEVEN

Dark Secrets Behind the Discovery of a Wonder Drug

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To the researchers in science
who did the hard work, and never
reaped the glory.

Complete honesty is of course imperative in scientific work.

—W. I. B. Beveridge, *The Art of Scientific Investigation*, 1957

PART I • The Discovery

1 • Zones of Antagonism

EVERY DAY AT DAWN IN THE summer of 1943, a young graduate student could be see striding briskly across the peaceful campus of the College of Agriculture. He was short, wiry, an handsome, his sharp features focused intensely on his important mission. Even his clothes seemed a afterthought, a wrinkled white shirt and loose gray pants, worn and reworn like those of any devote researcher surviving on a meager stipend and the excitement of his work. He came from the directio of the Plant Pathology greenhouse, where students were breeding new varieties for President Frankl Roosevelt’s Victory Gardens. He hurried past the dairy, with its herd of experimental Holsteins, pa the poultry house, where Rhode Island Reds competed with white Leghorns for egg-laying prowes and finally arrived at the Georgian-style Administration Building, which celebrated the proud coloni history of Rutgers University.

Albert Schatz, the harried student, was the first to arrive each day at the Department of So Microbiology. He let himself into the empty building and descended quickly into the baseme laboratory. He pulled on his long white lab coat made of heavy cotton, worn haphazardly like h clothes and with a tear down one side. Then he began work on his experiments, searching for ne antibiotics among the microbes he had found in the farmyard soil.

On that morning of August 23, he sat at his workbench and opened his notebook. On page 32, in h meticulous cursive, he entered the date and the title of his new experiment, “Exp. 11 Antagonist Actinomycetes.” Then underneath, with the precision of a ledger clerk, he wrote, “Control soils No 2, 7A, 18A, leaf compost, straw compost and stable manure plated out on egg albumin agar. Transfe made from colonies of actinomycetes selected at random ... by casual macroscopic observation.” An he added, for accuracy, “Some actinomycetes obtained from plates of swabs of chickens’ throats from Miss Doris Jones.”

It was the fourth summer of the world war and, although the New Jersey college farm w thousands of miles from the front lines, almost everything, even the plants in the greenhouse and th microbes in the soil, had some link to the war effort. Schatz had come to the college because h wanted to be a farmer, but now, aged twenty-three and at the start of his doctorate career, he foun himself engaged in a special war-driven mission. Instead of hunting for microbes that could brea down soil to make it more fertile, Schatz was part of a scientific race to find microbes capable producing new and more powerful antibiotics. His Experiment 11 was a routine test, one of hundre being made by other graduate students working on this nationwide project, but it would be much mo than that.

By 1943, Eleven U.S. drug companies were producing penicillin, the first antibiotic, discovered b Alexander Fleming in 1928. The first vials of penicillin were being rushed to the front to tre common infections from battle wounds. But in this war, a new threat had emerged: biologic weapons. Allied intelligence reported that Germany and Japan would not hesitate to use bombs an shells filled with deadly germs like anthrax, cholera, typhoid, and even the plague. Penicillin had n effect on such diseases.

The researchers best suited to the task of finding new antibiotics were not at medical schools, but the agricultural colleges. “Aggies” like Albert Schatz were quite familiar with microbes from the so that were capable of producing a chemical toxin that killed off the harmful bacteria that might be us in biological weapons. Each time they grew these microbes in a petri dish, they saw the telltale cle ~~zones, or “zones of antagonism,” as they were known, killing fields measured in millimeters~~ whe one microbe battled another for space or food. If they dropped penicillin into a petri dish of typho bacteria or cholera or the plague, no clear zones would develop. For this job, a stronger antibiotic w needed, the kind that Albert Schatz was hoping to find.

The basement laboratory where Schatz worked was primitive and sparsely equipped, grim even b the utilitarian standards of the times. But to this determined young man it was a hideaway, a plac where he could work uninterrupted. And he had volunteered for this isolation. His ambitious Ph.D. ha two parts: One was to find antibiotics against cholera and typhoid; a second was to find a cure for th deadliest of all infectious diseases, tuberculosis. Over the previous two centuries, two billion peop had died from tuberculosis, caused by a slow-growing, pickle-shaped microbe, *Mycobacteriu tuberculosis*. It was highly contagious, spreading easily from a victim’s sneeze or spit. Known as th “Great White Plague,” TB cut down rich and poor alike, although in the Industrial Revolution it sprea more easily in the crowded slums and factories. In wartime it spread quickly in bombed-out cities an crowded refugee camps. There was no effective cure. Doctors had tried everything from prolonge rest to fortify the body’s resistance, to drastic collapsed-lung surgery, to a range of alchemies and th new so-called sulfa drugs discovered by German researchers from industrial dyes. Albert Schatz professor, Dr. Selman Waksman, had warned of the risks. Waksman insisted that when Schatz handle the deadly TB microbe, he must work alone in the basement and never bring the germ to the labs o the third floor.

In recent days, Schatz’s laboratory had taken on the appearance of an ancient dispensary. In on corner an aging autoclave, a kind of pressure cooker used for sterilizing glassware, hissed awa Conical glass flasks contained rich dark brews of meat extract similar to gravy, a concoction Scha used to feed his microbes. On his bench were rows of petri dishes with microbe food in agar, th jellied extract of algae that microbiologists use for growing their molds. The microbes Schatz w cultivating came from the multicolored and somewhat mysterious group known as the actinomycete or “ray fungi.” These are strange, thread-like creatures that first appeared more than four hundre million years ago. They have wispy hyphae like the tentacles of a jellyfish, half bacteria and ha fungus, a sort of evolutionary link between the two. They were favorites of Dr. Waksman, an common in the farmyard soil, and they had already shown promise in producing antibiotics. The form strikingly beautiful colonies of blues, reds, and grayish greens, and in the soil they a responsible for the pleasant odor of earth after a light rain.

Albert knew where to look for them. His favorite hunting grounds included the compost heaps moldering leaves and twigs outside Plant Pathology, and the college stables, where he filled pots o fresh horse manure. The richest for his experiments, he knew, was the freshest—less than twelv hours old. Each gram of soil or compost Schatz collected was teeming with millions of differe microbes, but always some actinomycetes. He diluted the soil with tap water and let drops of th mixture fall onto petri dishes containing microbial food in the jellied agar. Then he incubated th dishes and watched the actinomycetes grow. Within a few days, he had good colonies of mold in h petri dishes. Some of them were surrounded by the telltale clear zones, indicating that they might b antibiotic producers. He chose his likely candidates for their robust look and their widest zones antagonism, like a gardener spotting a sturdy shoot, or a farmer selecting a high-yielding crop f breeding. Then he tested them for their action against known disease-producing bacteria from th same group as the typhoid and cholera germs.

By mid-September, he had selected two strains of a species of a gray-green actinomycete name *griseus*, Latin for “gray.” One strain had come from heavily manured farmyard soil and he named

18-16, for the sixteenth strain of the eighteenth soil sample. The other came from a colleague, Dor Jon~~es, as he had noted in his lab notebook. He named her strain D-1, for Doris. Much quicker t~~han h had dared to hope, Schatz had become convinced that he had discovered a new antibiotic, the first be found in the Department of Soil Microbiology for several months, and everyone was excite especially Dr. Waksman.

But no one could yet know whether his discovery would be useful as a medicine; if it was powerf enough to destroy typhoid and cholera it might also destroy human body cells. And it was only th first stage of Schatz's project; he still had to see if his new antibiotic would be effective against th toughest germ that causes TB. Schatz checked and rechecked Experiment 11, running the same tes over and over again until he was sure that he had not made a mistake. Each effort was careful recorded in his lab notebook.

By the middle of October, he had confirmed that 18-16 and D-1 were indeed behaving like goo producers of a new antibiotic. On October 19 at two o'clock in the afternoon, he placed a culture of h *Actinomyces griseus* in a test tube and sealed it for posterity by heating the end over a Bunsen burn and twisting the glass shut. That weekend, he wrapped the tube in cotton wool, put it in his pocket, an caught the train from the Rutgers University town of New Brunswick to Newark, then the bus Passaic, where his parents lived in a working-class section of the textile town on the Passaic Rive There, he showed the test tube to his father, Julius, and his uncle Joe and presented it to his mothe Rachel. She had not finished grade school and had no real idea what the test tube represented. He to her that he had found a new medicine that might eventually fight the infectious diseases, maybe eve tuberculosis, that she had seen too often destroying the lives of her friends and neighbors. That sh could understand.

2 • The Apprentice and His Master

The schatz family came from the peasant class in the old Russia, and their entry into America an immigrant story of the kind often told at the turn of the twentieth century. Albert's grandfathe Shlomo (Sam) Schatz, was a butcher, and his grandmother's family, the Tunicks, were known for the physical strength and much revered in the community for forming local vigilante committees defend Jews during the pogroms. Sam himself was a strong man who once, legend has it, leaped on bull that was running amok through the village and wrestled it to the ground. But Russia was a barre and hostile place, especially for Jews, and Sam left his village on the outskirts of Minsk in 1899 ar immigrated to America, leaving his pregnant wife, Rose, and their five children with her fathe Ephraim. He arrived at Ellis Island and moved in with a cousin on Manhattan's Lower East Side. took him five years, working as a house-painter, to save enough money to bring his family, includir Albert's father, Julius, to New York.

The family lived in a walkup, and soon after their arrival one child died of a weak heart. Th moved into a Brooklyn tenement, and Sam and Rose had six more children, but the man who cou wrestle a bull grew weak from heavy smoking and living in the putrid city air. When doctors told hi he should leave for a life in the country, the Jewish community had just the answer.

Baron Maurice de Hirsch, a German-born Jewish banker, gave mortgages to immigrant Jews enable them to build their own barns and homes. He also set up the small Woodbine Agricultur College in New Jersey to produce "intelligent, practical farmers." With the help of Hirsch funds, Sa Schatz bought a dirt farm in Fitchville, Connecticut, joining other Jewish settlers in sma communities across the state. On most of these farms the soil was poor, exhausted by Yankee farme who had abandoned it to move west or, in some cases, for better jobs in the cities.

The Schatzes were the first Jewish family at Bird's Eye View Farm, a stone house, two woode barns, and a manure pit built on a rise known as Cannonball Hill. The family scratched a living from dozen milk cows and some chickens. They sold vegetables in the spring, and in the summer they too in boarders from the city. While the urban renters lived in the farmhouse and enjoyed the gre outdoors, the Schatz family lived in tents. Julius joined the U.S. Army in World War One, and after h returned, he was delivering vegetables by horse cart to nearby Norwich one day when he met a prett dark-haired young woman named Rachel Martin who worked in a bakery. They soon married. H parents were Jewish immigrants from Poland who had come to America via Britain.

On February 2, 1920, Albert Schatz was born in a Norwich hospital. The family stayed on the far until he was three, when they moved to Passaic, New Jersey, where Julius's sister Rebecca and he husband, Abe, had a grocery store. They lived in a wooden three-story house with six apartment three at the front and three at the back. Two girls were born, and the family moved back and for from Passaic to the farm, wherever there was work. As soon as he was able, Albert helped out on th farm. He learned how to sharpen farm tools, milk cows, make butter and cheese, and drive the hor cart. When he was older, he shot groundhogs, mended his own clothes, and darned his socks. H attended the local one-room school-house, which had one teacher and twenty students, grades o through eight. The building was twenty by twenty-five feet and had two entrances, one for boys ar one for girls. Albert wanted to be a farmer, like his father and grandfather.

During the Great Depression the family lived mostly in Passaic. They joined other immigran from Eastern Europe—Hungarians, Czechs, Poles, and Russians. Albert witnessed much poverty ar sickness, people fighting for scraps on the garbage dumps and dying from infectious diseases, lil ~~pneumonia, diphtheria, and, of course, tuberculosis. It was a raw and sometimes violent period.~~ One the young boy's lasting memories was of the bloody police charges that ended the fourteen-montl long Passaic textile workers' strike involving fifteen thousand workers, in 1926–27. The polic dispersed the strikers with horses and water cannons, and schools were often closed. Despite tl disruptions, Albert managed to stay in classes and was a consistently promising student at Passa High School.

Albert Schatz, age twelve, with his mother, sisters Sheila and Elaine, and his maternal grandmother c the Connecticut farm in 1932.
(Courtesy Vivian Schatz)

In his junior year, in 1936, when he was sixteen, he contributed three paragraphs to the scho newspaper about his "life's ambition," to be a farmer. He did not seek wealth "for I should not kno what to do with it." He wanted to "sweat by honest labor" and to "roam the open fields." He wanted chop wood until his muscles ached. "I want to LIVE."

Aged eighteen, Albert won a scholarship to the Rutgers' College of Agriculture, the first in h family ever to attend an institution of higher learning. In his second year, he was elected to Phi Be Kappa, a rare achievement for an "aggie." The head of the Department of Soil Microbiology, D Waksman, was another Jewish immigrant of Russian descent. He was always on the lookout for brigl young graduates, and was happy to accept Albert as a Ph.D. candidate.

SELMAN ABRAHAM WAKSMAN, the man behind the intense wartime hunt for antibiotics Rutgers, was no ordinary soil scientist. Like the Schatz family, Waksman had arrived in America a the beginning of the twentieth century, but he came from a different social order and had achieve much in the New World.

He was born on July 8, 1888, according to the old Russian calendar, in the small market town c Novaya Priluka, in western Ukraine, two hundred miles from the regional capital of Kiev. He wrote his memoir that it was "a mere dot in the boundless steppes," surrounded by chernozem, the ferti black earth on which wheat, rye, barley, and oats flourished, as long as the rains came. Without ther famine swept the land. The inhabitants of the small towns and villages of Western Ukraine wer

recently freed serfs who scratched a living from smallholdings, and Jewish artisans and tradesma
who marketed the farm and forest products.

His life there was simple, but not uncomfortable. His father was the relatively well-off son of
coppersmith and had inherited property. His mother was the daughter of a successful businesswoma
who ran a dry goods store, a "prominent merchant in the community." His mother had inherited th
store, and together his parents were able to pay for Selman's private tutors.

Immediately after marriage, his father had been drafted, like all able-bodied men, into the czar
army for five years, leaving Selman's mother to carry on her business and fend for herself. When h
father had returned from service, Selman had been born, but his father showed little interest in bein
with his son, most of the time living twenty miles away in the nearest large city, Vinnitsa, where h
had inherited property. Selman was brought up by his mother, several aunts and maiden cousins, an
his maternal grandmother, who had eight daughters. Selman was the son of the youngest daughte
Inevitably, he was spoiled.

His mother taught him to read and sent him to the local heder (private school) and then to priva
tutors. She also made sure that he studied the Bible and the Talmud. The young Selman quick
learned Hebrew and Russian literature, history, and geography. And he was frequently picked as th
one to read a chapter from the Bible or deliver the blessing on the initiate at a bar mitzvah.

Jews and Ukrainians lived side by side in Novaya Priluka. The Waksmans lived in the wealthie
part of town. His mother gave birth to a daughter when Selman was seven, but the daughter died le
than two years later of diphtheria.

In the Waksman household there was usually money left over to help a needy niece or nephew, o
the less fortunate on the town's poorer side. Encouraged by his mother, Selman gave free lessons i
Hebrew and Russian, and later private lessons to the sons of the wealthier inhabitants and the riche
peasants.

The first Russian uprising of 1904–05 did not affect little Novaya Priluka, but revolution was in th
air. Selman's friends were divided on the future. One believed that socialism was inevitable, an
another, the Zionists, looked for salvation in a new homeland in Palestine. Selman was uncommitte
with divided sympathies—on the fringe of the two groups. Instinctively, he favored th
revolutionaries, but he disliked the fierce arguments over the form of a future government, should
revolution be successful. He was more interested in pursuing a higher education, but the way w
blocked because he was a Jew. He could not enter the gymnasium or go on to university witho
passing a special competitive exam.

In 1908, he left with four friends for Odessa to be coached, at a price, for the crucial exam. H
passed "with flying colors" and returned home a hero now set to attend university in Odessa. B
suddenly he suffered a terrible blow. In the summer of 1909, his mother died of an intestinal blockag
During the seven days of mourning, he read and reread the Bible, "perhaps for the last time."

He returned to Odessa to find new political barriers. Candidates for the university had to have bee
born in Odessa or have spent the last twenty years there. Selman managed to bribe a governme
official to give him the necessary papers, but when his friends were refused admission, they a
decided to leave Russia for good. He thought briefly of going to Switzerland, a destination favored b
his father, but his cousins in Philadelphia, having heard of his mother's death, urged him to join them

In October 1910, Selman and a group of five young people from Novaya Priluka, three men and tw
women, left by train for Bremen, and thence for America. They landed in Philadelphia on Novemb
2.

BY THE BEGINNING of the twentieth century more than three million Russians had immigrated the United States. Waksman, now aged twenty-two, went to work on his cousin's five-acre farm nea ~~Metuchen, New Jersey, thirty miles from New York City. He helped with the hens, learned h~~ow t make compost from stable manures, and planted vegetables in the spring for local markets. His cous was a great teacher, and at the end of his first year Waksman published an article in the *Rural Ne Yorker* titled "How I Raised a Flock of Chickens," for which he was paid his first ten dollars.

Selman Waksman as he was about to leave Russia in 1910. (Special Collections and University Archives, Rutgers University Libraries)

But his goal was college. He thought of becoming a doctor, and was accepted at Columb University medical school. Another cousin, who was a dentist, offered to help with the fees, b Waksman did not want to be tied down by debt.

So he had to take what was available, and in those days the most accessible institutions were t land grant colleges. These were created by the Morrill Act of 1862, which gave states land grants fund public agricultural and engineering colleges. One of the first such establishments was at Rutge College, established originally as Queen's College in 1766 and still a small institution at the turn the twentieth century.

Rutgers was only eight miles from Metuchen, and Waksman's farmer cousin suggested he shoul go and see Jacob Lipman, another Russian immigrant, who was then head of the Department Bacteriology. By 1911, Lipman was an established figure in soil science, having made his reputatio on studies of bacteria that make nitrogen available for crops.

Waksman was persuaded that a course in agriculture would satisfy his curiosity about t biochemistry of living organisms, plus he was awarded a full scholarship. Aged twenty-three, he foun it hard, at first, to be among much younger boys of seventeen, who teased him for his clumsy Englis and dislike of sports. He also found the level of teaching poor. In his sophomore year, his chemistr professor was "an unimaginative bore," physics was "a great disappointment," he found the courses American and English literature uninteresting, and he disliked Shakespeare. The French teacher w enthusiastic, but he felt he already had enough knowledge of foreign languages. The only courses th earned his approval were zoology and botany.

At the end of his second year, he yearned for independence and moved into a room in an old hous on the college farm, paying for his accommodation by working in the college greenhouse and helpi out in the laboratory. He bought cracked eggs from the Poultry Department at eleven cents a dozen.

Another and more important reason for striking out on his own was the arrival in New York fro Novaya Priluka of a young woman named Deborah Mitnick. The daughter of a prosperous gra merchant, she was the sister of Waksman's best friend, Peisi, back in Ukraine, and after finishin ~~grade school she had come to stay with her cousins, braving the voyage from Riga on her own~~ in th middle of winter. She was good looking, bright, and energetic. In America, she quickly joined Peisi i New York—he had come to America with Waksman, in 1910. She worked in a sweatshop, became member of the International Ladies' Garment Workers' Union, and took singing lessons. She wa affectionately known as Bobili, Russian for young grandmother, a nickname given in the hope that sh would reach a ripe old age. Waksman had been her tutor in Novaya Priluka, had always admired he and planned to marry her.

In his studies, Waksman had at last found a subject that interested him: general bacteriology unde Dr. Lipman. "I felt that I was finally under the tutelage of a master," he wrote. Waksman was the onl student majoring in soil microbiology. For his senior thesis he listed the different groups of microbe —bacteria and fungi—but he was fascinated by the actinomycetes. He dug trenches on the colleg farm and mapped the different horizons of the microbes he found in the soil. He took samples fro each layer, suspended them in water, put the microbes on petri dishes of nutrient agar, let them gro for a week, and then counted the different colonies that had developed.

The actinomycetes, hardly noticed in America, had been known for more than forty years Europe, having first been described by German researchers as a microbe responsible for a disease cattle known as "lumpy jaw," literally lumps on the animal's cheek containing a growth of th microbe. Russian researchers had also published papers on the actinomycetes, and Waksman had distinct advantage over his colleagues because he could read German and Russian. He cataloged th different species and played an important role in their early classification into five genera, dependin on a microscopic examination of the degree of branching of the cells, whether they produced spores chains or singly on stalks, and whether they could live with or without oxygen. Thus, as Waksma would write forty years later, began his interest "in a group of microbes to which I was later to devo much of my time and which were to remain for the rest of my life as my major scientific interest."

He was elected to the scholastic fraternity Phi Beta Kappa, and on his graduation in 1915, Lipma offered him a job as a research assistant in soil microbiology and a stipend of fifty dollars a mont which in those days meant he could continue to live comfortably in his room in the farmhouse an study for his master's degree.

By the end of 1915, he had written his first academic paper on bacteria, actinomycetes, and fungi the soil. He was twenty-seven. The paper was published in February 1916, the year he became American citizen and the year he married Deborah "Bobili" Mitnick.

Selman Waksman married Deborah Mitnick, his childhood sweetheart, in 1916. (Special Collection *and Archives, Rutgers University Libraries*)

"I had sent my roots into the soil in search of its microbiological population," he later wrote. "I w now on my way. I knew now exactly what I wanted and how to get it. The rest was merely to follow plan. California was to prove whether I was on the right track."

The new couple moved to the University of California at Berkeley, where Waksman studied for tw years for his doctorate on the enzymes produced by microbes, mostly the actinomycetes. During h last year he supplemented his income by working at Cutter Laboratories, a local commerci laboratory producing antitoxins and vaccines against bacterial infections. It was the start of a lifelo connection between his research as a microbiologist and industry.

3 • The Good Earth

IN THE SUMMER OF 1918, AS World War One was drawing to a close, Waksman returned t Rutgers to take up a new position as the farm college “Microbiologist.” His somewhat mundane tas was to continue the search for microorganisms that would produce more fertile soils, but he insiste on the rather grand title, with a capital *M*, as a mark of the importance he attached to the emergin science, and his own place in it.

The war had taken its toll, even on the quiet backwater of the New Jersey Agricultural Experime Station. There were no graduate students and no lab assistants in the Department of So Microbiology. Waksman found the laboratory benches covered with dirty petri dishes, and the cultur of fungi and actinomycetes he had put into the culture collection before leaving for California we either dead or in need of prolonged resuscitation.

The sorry state of the laboratories reflected the scarcity of funds. His mentor, Dr. Lipman, coul offer him only one day a week and fifteen hundred dollars a year, less than he had been getting as part-time bacteriologist in the Cutter Laboratories in California. Personally, he had no funds reserve, and he was forced to look for another part-time job in industry to supplement his income. did not present a problem.

Before the war, America had been dependent on Germany for supplies of chemicals, laborator glassware, and even scientific literature, but was gradually severing these ties and establishing its ow infrastructure of scientific research. Waksman was now a bacteriologist and a biochemist, a goo combination for employment amid the expansion of microbial research after the war. The brewery an food industries were studying yeasts and cheese-producing molds, public health officials were lookin at new ways to use microbes in sewage disposal, and drug companies were beefing up their researc into medicines to cure infections. In agriculture, researchers concentrated on identifying soi enriching microbes to grow bigger and better crops.

This bustling activity was a natural progression of the work of the nineteenth-century Europea pioneers of bacteriology—Louis Pasteur, who first formulated the germ theory of disease, and th German bacteriologist Robert Koch, who discovered the TB microbe. On the eve of World War One German researchers had found a new purpose for the dyes that had been used to identify bacterial cel under the microscope. In 1910, a young German chemist, Paul Ehrlich, and his Japanese assistan Sahachiro Hata, found an arsenic-based dye that worked against the syphilis microbe. They named salvarsan, and it became the first of the so-called magic bullets that would cure bacterial infections.

From among the many companies making offers, Waksman chose the Takamine Laboratory, i nearby Clifton, New Jersey, one of the more successful of the new companies producing antibacteri products, including salvarsan. Waksman’s job was simple enough for a postgraduate biochemist—h had to test each batch of salvarsan for toxicity to human cells. He was paid good money for tho days, forty-five hundred dollars a year, and the company was close enough to Rutgers for him combine his work with a day a week at the college. The money even allowed him to move in Manhattan, where his wife, Bobili, could enjoy the music, theater, and culture missing in rural Ne Jersey.

Over the next two years, Waksman was exposed to much more than how to test a drug for toxicit The Takamine Laboratory produced and marketed adrenaline, a natural product of animal adren glands. His experience “suggested the possibility” of finding other useful natural products—perhap even among his favorite microbes, the actinomycetes.

Waksman was a rising star in microbiology at a time when researchers were focusing on a ghoulis question. What became of all the microbes that caused deadly diseases—typhoid, dysentery, choler diphtheria, pneumonia, bubonic plague, and tuberculosis—when a dead body was buried in the earth When scientists searched the nearby soil, they found few of these germs, and they concluded th either the microbes could not exist in the soil, because the environment didn't suit them, or they we consumed by predators larger than themselves, or, a far more intriguing possibility, they wer destroyed by other microbes.

In London at the turn of the twentieth century, researchers found that the cholera bacterium, *Vibr cholerae*, survived in clean, deep water but not in surface water containing microbes present in the a Cholera bacteria disappeared quickly, in a matter of hours, in sewage sludge, and also in seawater. *coli* was rapidly crowded out in manure piles teeming with other species of microbes. On the microbe battlefields, researchers in Europe and Australia found actinomycetes to be active warrior but Waksman was reluctant to become involved. He had no medical training and preferred t concentrate on microbes that were useful in agriculture.

When finances at Rutgers improved in the early 1920s, Waksman became a full-time assista professor in his chosen pursuit—the microbiology of the soil. The condition of his labs was st pitiful, and he complained to Dr. Lipman. The division of soil chemistry had only two workers but ha "three laboratories and three large closets," and his division, soil microbiology, "had four workers an only one laboratory." Recent alterations to the Administration Building had not included painting h walls, which "absolutely demoralizes the assistants and discourages the workers," he wrote to Lipma

In 1923, Waksman and his graduate assistant, Robert Starkey, saw actinomycetes producing clea zones when matched against other bacteria. "A zone is found free from fungus and bacterial growth their joint paper concluded, and "numerous" microbes, including bacteria, fungi, and actinomycete "bring about injurious or destructive effects upon themselves or upon other soil organisms." B Waksman was interested only in the effects on the fertility of the soil. He did not link this strang activity to the possibility of curing human infectious diseases. "Unfortunately our own observatio on the growth inhibiting effect of actinomycetes upon other microbes were not pursued further at th time," he later wrote.

In 1924, Waksman took six months off from Rutgers to go to Europe on a "grand scientific tou with his wife and their four-year-old son, Byron. It was the first of five European tours that he wou make with his wife before the outbreak of World War Two. In 1924, the main attraction was conference on soil science in Rome organized by Jacob Lipman, who allowed Waksman to continue t be paid his small Rutgers salary but gave him no expenses for the trip. Despite his tight budge Waksman packed in a hectic schedule of visits to major soil microbiology laboratories in Britai France, Germany, Sweden, and Holland. In Paris he met and struck up a thirty-year friendship with th Russian pioneer of soil microbiology, Sergei Winogradsky, now an émigré in Paris. And in Holland h visited Martinus Beijernick, who made his reputation by discovering viruses in 1898 and went on find bacteria that make nitrogen available to plants. According to Waksman, Beijernick greeted hi with the words "You are the actinomyces man." Waksman also went to Moscow and even h hometown, Novaya Priluka, in Ukraine. There he witnessed the ravages of the revolution and the civ war and saw again the little house where he was born. "It looked like a hole of a troglodyte," he wro later. He returned to America determined to write source books to fill the gaps in the literature of so science.

"I was primarily a soil microbiologist," he wrote, "studying soils and composts, peat bogs an manure piles ... concerned with products of microbes that are used in green plants." He "scarce dreamed of becoming profoundly involved in problems dealing with human health.” He was “too bus ~~completing [his] work on the distribution of different groups of microorganism in the soil,~~ their ro in the decomposition of organic matter and formation of humus.” His studies resulted in several maj works that said almost nothing about the possible medical application of his fighting microbes.

In a 360-page book, *Enzymes*, published in 1926, he devoted only one paragraph to antagonist bacteria. In his 894-page tome *The Principles of Soil Microbiology*, he wrote only two pages c “antagonism and symbiosis among microorganisms.” On another page, he mentioned the “inhibitiv effects” of fungi and actinomycetes. In a smaller book, *The Soil and the Microbe*, written wi Starkey, now Waksman’s deputy, in 1931, they discussed the role of microbes in the life cycle of so organisms. But he wrote only one sentence about bacteria fighting among themselves.

In his lectures and scientific papers, he would remind his students and readers that the soil was complex system, our knowledge of it limited, our methods crude, and we were still unable understand how it works. In the basement lab, his students followed “a semi-military regime,” ofte working weekends during the depression years because they had no money to spend. They wrote bri descriptions of each day’s projects in five-by-seven-inch lab notebooks, which Waksman reviewed the beginning of each week. One student recalled what was known as the “book parade.” “Waksma would spot Harry and say, ‘Let me see your book.’ Waksman would glance at it and add, ‘Tell Dave t bring his book.’ Harry, disarmed, would go down to the basement lab and pass the word. Dave woul submit his book and come back to order another student up to the office. The books were return when Waksman spotted an error, or something unclear, but he never accused anyone of being a slo and all partings were amiable. The book parade seemed to me a little Teutonic.” Waksman rarel visited his students in the basement lab, even then. But once a year he held a spring cleaning, which l obviously enjoyed. All drawers and cabinets had to be open for inspection, and Waksman would wal in followed by his assistant, who carried a laundry basket. The student wrote, “If he found equipme lying on the bench, or chipped, or unlabelled, he would say, ‘Vat’s this for?’ in his Russian accen (which he never lost) and if there was any doubt, he would tell his assistant, ‘Throw it in the basket.’

In those days, Waksman’s students were still not looking for medical applications. “The soil ar the microbe,” Waksman wrote, “await the investigator [who] is not looking for practical gains but fo explaining the obscure and observing the unknown. The application will doubtless come Undoubtedly, Waksman missed a great opportunity. Had he pursued what he had observed wit Pasteur’s “prepared mind,” he, not Alexander Fleming, might have been the first to discover a antibiotic.

But he was not a physician, like Fleming, and Rutgers had no medical department. In his daily lif Waksman was not exposed to faculty discussions about the therapeutic value of “magic bullets” lik salvarsan, or the sulfa drugs that followed. In 1932, the German doctor Gerhard Domagk, working the giant chemical company I. G. Farben, found a bright-red dye that cured mice infected wi pathogenic streptococci. This new compound, named Prontosil, was good for fighting a wide range bacterial infections and later gave rise to the sulfonamides, or sulfa drugs, which had a major impa on the treatment of infectious diseases. (The life of Winston Churchill was saved by a sulfonami when he developed pneumonia after the Tehran Conference with Stalin and Roosevelt at the end November 1943.)

Yet Waksman still lacked funding to expand his research. In America, medical research, like othe scientific research, suffered from a lack of public assistance. In the 1920s and ’30s, the Nation Institutes of Health and the National Science Foundation did not exist. Waksman relied on his wits attract support. He was a good salesman, a scientist-entrepreneur who never seemed short of indust sponsors.

He helped tanners find enzymes for defatting hides; brewers, enzymes to clarify beer. He convinc the ~~local mushroom industry that providing funds to investigate a compost mix of alfalfa,~~ pean shells, and tobacco stalks was a better bet than relying on horse dung from the declining stables of th Philadelphia police department. These links with industry provided rare funding during the depressio years, and endeared Waksman's graduate students to him for providing them with beer and mushroo tastings. There were some unexpected delights. On one famous evening in the college auditoriu female models paraded in then-daring off-the-shoulder evening dresses with fringes of miniatu orchids bred in Dr. Waksman's Department of Soil Microbiology. The event was sponsored by a loca businessman hoping to sell the orchids at debutante balls.

A few independent foundations gave research grants, and in 1932, the National Tuberculos Association funded Waksman to study the fate of TB germs in people and animals who died of TB ar were buried in the soil. He assigned the task to one of his graduate researchers, who found that th tuberculosis bacteria were greatly reduced in some soils. But Waksman did not follow up th interesting result. Similar results were being obtained by other researchers, and Waksman thoug they all seemed to lead nowhere. He was not "yet prepared to take advantage of these findings."

In late 1935, Fred Beaudette, Rutgers's director of Poultry Pathology, brought Waksman a test tub containing a TB bacterium specific to poultry that had been destroyed by a fungus that ha accidentally contaminated the tube. This was indeed a "happy accident" of the kind that Fleming ha encountered seven years earlier with penicillin. Yet Waksman was still not ready to seize th opportunity, this time staring him in the face.

There was, of course, a perfectly good and understandable reason for not wanting to test microbe's ability to destroy pathogenic bacteria: the risk of catching the disease. In his writing Waksman never mentions this as a factor, but it must have been on his mind. His underfunde laboratories were poorly equipped to protect the workers against infections, or even the hazards handling dangerous chemicals. In the basement laboratory, protective clothing consisted of worn ar torn white lab coats and some "very crusty, black, rubber lab aprons designed to catch splashes of h acid." These coats were "hung on spikes driven into the wall" when not in use.

BUT WAKSMAN COULD not ignore the research coming out of Europe and Russia. In the mi 1930s, the Russians led the world on research into the antagonistic properties of Waksman's preciou actinomycetes. By 1935, Russians had published four papers on the subject; Waksman had publishe none. A key Russian paper reported that actinomycetes were antagonistic to *Bacillus mycoides*, one the standard bacteria tests for antibiotics. The paper concluded, "The question of interrelationships soil microbes deserves profound research." Waksman had an enormous advantage over his peers America in being able to read these papers, not just the English summary that was always included b the whole paper, and some have speculated that the Russian research started to turn his mind towa the possibility of antibiotics, a suggestion he never acknowledged.

In 1936, at the Second International Congress for Microbiology in London, Alexander Flemin discussed the antibacterial properties of his penicillin, a debate which Waksman later listed as a important event in the evolution of his own thinking. One of Waksman's graduate students recalle that Fleming's discussion was when Waksman became "seriously interested" in antibiotic research.

Later in 1936, Waksman began to study the published papers on warrior microbes and wrote tw papers for *Soil Science*, the journal started at Rutgers by Dr. Lipman. The first paper reviewed th current literature, including the four Russian papers. A measure of Waksman's absence from basi research in this area is that of the 107 papers he listed, only 2 were written by him.

In the second paper, also finished in 1936, Waksman and a graduate student, Jackson Foster, teste a fungus, a bacteria, and an actinomycete from a Scottish peat bog. They were all capable of producin “substances which are antagonistic” to other soil microbes when grown in petri dishes containin artificial nutrients. In 1937, another Russian researcher found that antagonistic actinomycetes we “widely distributed” in different soils in the Soviet Union. Of eighty cultures isolated from variou soils, forty-seven possessed antagonistic properties, but only twenty-seven were found to be capab of liberating toxic substances into the nutrient agar on a petri dish.

In 1938, Waksman was especially influenced by the work of one of his former students, Ren Dubos. A Frenchman who had qualified in agriculture and immigrated to America in 1924 afte hearing Lipman speak at the conference on soil science in Rome, Dubos worked for his Ph.D. und Waksman at Rutgers. He discovered a soil microbe that produced an enzyme capable of breakin down cellulose, the key ingredient of plant stalks and tree bark, and turning it into plant food. Simil work was being carried out at the Rockefeller Institute for Medical Research, in New York City, whe Dubos later moved. There, he eventually isolated a bacterial enzyme that destroyed the sugary coat the bacteria that causes pneumonia. Unfortunately, the enzyme was too toxic to be used by human suffering from pneumonia, but Dubos was sufficiently encouraged to begin the first systematic searc for antibiotics in the soil.

In 1939, he found an antibacterial agent produced by a bacterium, *Bacillus brevis*, and named tyrothricin. The Rockefeller biochemist Rollin Hotchkiss helped him recognize that it was made up two compounds, tyrocidin and gramicidin. Tyrocidin was toxic to mice, but gramicidin cure experimental infections in mice, without side effects. Gramicidin was too toxic to be administered humans intravenously, but it was effective when used on open wounds. The Russians produced the own version of Dubos’s discovery, known as gramicidin S (for Soviet), and used it throughout Worl War Two as their main antibiotic.

That same year, the Russians struck again. Two researchers, N. A. Krassilnikov and A. Korenyako, again found that many species of actinomycetes produced antibiotics. The Russian concluded that “one cannot escape the possibility of using the bacterial factor of actinomycetes” treat bacterial diseases. For the first time, they discovered two that were active, ever so slightl against *Mycobacteria*, the group that causes tuberculosis. To anyone searching for a cure for TB, was a powerful clue that such an antibiotic might be found.

By late 1939—in the wake of pioneering research by the Russians, a major discovery by Dubos New York, and the beginning of the war in Europe—Waksman, the soil microbiologist who ha pledged his life to microbes that could be used in plants and industry, was finally ready to change th direction of his research to look for antibiotics to cure human diseases. All he needed was a sponsor.

4 • The Sponsor

Twelve miles down the railroad track from the Rutgers campus is Rahway, New Jersey, once a old Indian settlement and a stop on the stagecoach run from New York to Philadelphia. Since 190 Rahway has been the home of Merck & Co., then and now one of the most important pharmaceutic concerns in the country. Friedrich Jacob Merck opened the original family-owned apothecary, th Engel-Apotheke (Angel Pharmacy), in 1656 in Darmstadt, Germany. In 1827, the Merck compan started producing morphine, codeine, and cocaine. By the 1890s, Merck was selling so many produc in America that the family dispatched the twenty-four-year-old George Merck to set up shop there. H settled in Manhattan, bought 150 acres of Rahway, and later sent his son, George Jr., a blond, blu eyed giant at six feet five inches, to Harvard. On George Sr.'s death in 1926, his son took over th business.

By the beginning of World War Two, Merck was also producing vitamins. First came vitamin B1 Until the Merck chemists figured out how to synthesize the compound, tons of rice bran went into o end of Merck's Rahway plant, and fractions of an ounce of vitamin B1 came out the other end. Soo there was vitamin B2 for pellagra, vitamin B12 for anemia, vitamin C for colds, and vitamin A f eyesight. George Merck was also keeping a watchful eye on the Rutgers Department of So Microbiology. Like many other microbe researchers, Selman Waksman was experimenting with way to use fungus fermentations to make citric acid, used in foods and soft drinks, and fumaric acid, us in dry cleaning.

At the beginning of 1939, Merck engaged Waksman as a consultant on microbial fermentation, fi at $100 a month and then $150. In the summer of that year, Merck funded a $150-a-month stude fellowship specifically to find new ways of making citric acid. The program was successful, and th consultancy and the fellowship were renewed on an annual basis.

None of Waksman's students knew about his consultancies with Merck, not even his deputy, Bo Starkey. Some of the funds went into fellowships and stipends for his graduate students, some f "collaboration" between Merck and his laboratory, and some for "private consulting" between himse and Merck.

Toward the end of 1939, Merck expressed interest in hiring Waksman as a consultant o antibiotics, although in those days the word *antibiotic* was not in common usage. Merck called the "antibacterial chemotherapeutic agents." One such agent was penicillin. Although Alexander Flemi had discovered penicillin's antibacterial powers in London in 1928, he had never found a method o storing, concentrating, or purifying it, and it had remained a laboratory curiosity.

American scientists had read about Fleming's discovery, and in 1933 a graduate student Pennsylvania State College had studied Fleming's microbe for his doctoral thesis. He confirme Fleming's claims about the instability of the drug and, being unable to extract it himself, made n further investigations. Still, two other American drug companies, Eli Lilly and E. R. Squibb, looked penicillin's potential. Squibb researchers carried out their own literature search and produced a wel reasoned statement, now a classic in the history of penicillin, concluding that "in view of the slo development, lack of stability and slowness of bacterial action shown by penicillin, its production a marketing as a bactericide does not appear practicable." Penicillin was sidelined in favor of th readily available sulfa drugs.

In 1936, a chemist at Merck was shown a culture of Fleming's *Penicillium notatum* by a physici from New York's Beth Israel Hospital who predicted that more interesting antibiotics were on th way. ~~Three years later, Merck's research director, Randolph Major, asked Dr. Waksman's advice~~, and he suggested taking penicillin seriously. Other similar agents would probably soon be found, l forecast. Merck immediately hired three new staff members to "study isolation of therapeut substances from micro-organisms."

In Britain, the start of the world war had revived interest in Fleming's penicillin. At Oxfor University, Howard Florey, an Australian pathologist, and Ernst Chain, a German Jewish chemist wh had fled the Nazis in 1933, began work on purifying penicillin.

In the fall of 1939, Merck returned to Waksman with another proposal. This time the compan offered him a second consultancy—of another $150 a month—for information abo "chemotherapeutic agents." "I informed them of my own interest in antibiotics," Waksman note later. "They placed another fellowship in my laboratory and engaged me to help Merck in this field c research." Merck agreed to carry out "chemical, bacteriological and biological tests for th production, purification, plus identification and evaluation and to arrange for clinical trials." The were the kinds of tests that could not be carried out at Rutgers because of a lack of facilities. exchange, Merck would have the exclusive right to develop any new drug that resulted from th research. The company would pay Rutgers a royalty of 2.5 percent of net sales.

In August 1940, the Oxford team published their first promising results of the use of penicillin c ten patients, and the team was eager to start development. But British industry was overstretched, ar under constant air attack. Florey and a colleague, Norman Heatley, brought penicillin to America ar found a government not yet at war, and drug companies eager to be the first in the antibiotic marke Merck, Squibb, Lederle Laboratories, and Pfizer & Co., in the East; Abbott, Parke, Davis, and the Up john Company in the Midwest. Merck agreed to be part of a massive, U.S. government–sponsored w effort to produce penicillin. George Merck sent a telegram to Vannevar Bush, director of the Office c Scientific Research and Development: "Command me and my associates ... if you think we can he you." The Roosevelt administration launched an astonishingly successful example of governmer science-industry cooperation, second only in wartime to the atomic bomb project. It would eventual involve ten American and five British firms, combining efforts to make the drug for Allied troops.

George Merck of Merck & Co. with vial. (The Merck Archives, 2011)

WAKSMAN'S DEAL WITH Merck caused quite a stir in the offices of the Rutgers administratio They wanted to make sure the university got its share. Like many universities of the day, Rutgers ha no policy for dealing with faculty who made patentable discoveries. The most recent case, in 193 concerned a professor of pomology named M. A. Blake, a well-known breeder of peaches who wa called the father of the New Jersey peach industry. He was especially proud of his latest nectarin crosses and wanted to apply for a patent.

Whether Blake himself had the right to take out a patent depended on his contract, the Rutge lawyers advised. If he had been employed specifically to breed nectarines, he would have to assign th patent to Rutgers, but if he was a "general employee" in the fruit-breeding department, and he ha bred this spectacular new nectarine in the course of other work, then he would be entitled as a individual to apply for a patent and collect royalties. The lawyers noted, however, in view of Rutgers duty to make agricultural discoveries available for free to the public, that Professor Blake "might b embarrassed" if he started to profit from the patent. In that case, there was a third way: He cou assign it to the nonprofit Rutgers Endowment Foundation, a body originally set up to receive alum donations. A percentage of the royalties could be paid to the professor, the lawyers said, in line wit similar arrangements at other universities.

This quickly became Rutgers's policy; the only question was what percentage, if any, of th royalties to allow the discoverer. In 1937, Rutgers agreed to a 50-50 split—until it found out that was being overgenerous compared with other universities, or, as the Rutgers comptroller, A. Johnson, observed, that it had been "decidedly off on the wrong foot." Rutgers reduced th discoverer's share to 25 percent, but even that was above what other institutions were payin Purdue's was fixed at 20 percent, the University of Wisconsin's at 15 percent. Wisconsin's Alumn Research Foundation director, A. L. Russell, advised Johnson to "keep in mind" that university paten are "to be taken out primarily in the interest of the public rather than for the inventor."

While the Merck deal with Waksman was being worked out, the first of Waksman's graduat students to work on the antibiotic project arrived at the Department of Soil Microbiology. Boy Woodruff, a tall, confident, genial farmer's son from South Jersey, joined Waksman's laboratory i July 1939. His parents were determined that he should have a university education, but all they cou afford was the state-supported agricultural and engineering course at Rutgers. He lived with oth students above the chicken house, which at that time accommodated 125 white Leghorns. Woodru earned pocket money selling farm eggs.

Woodruff had found the college experience exciting and sometimes a little overwhelming. He ha gone to a concert for the first time, and had celebrated with his fellow students all night in 1937 whe the Rutgers football team scored its first victory, 29 to 27, over Princeton since 1889. He graduated soil chemistry, and Waksman offered him a college fellowship of $900 a year—20 percent more tha fellowships elsewhere. The money came from Merck's generous contributions to Waksman, no totaling $3,600 a year.

As a result of his European tours, Waksman attracted students worldwide. Eleven graduate studen crammed into the two upstairs laboratories of the Department of Soil Microbiology. They came fro China, South America, Europe, and across the United States. At first Woodruff was "terribl discouraged" when Waksman put him to work on composts and gave him little direction. He relie heavily on Waksman's deputy, Robert Starkey, as had most of Waksman's graduate students over th years. As one of them recalled, Starkey was their "great provider of materials and receiver complaints—the equivalent of an assistant in a steel mill. He remembered; he got things done. He to us how to make our cases to Dr. Waksman. Modest to a fault, totally loyal to the Department—it inconceivable that Dr. Waksman could have operated without him." Woodruff worked alongside visiting student from China who was trying to find out the minimum temperature needed to kill all th harmful bacteria in human feces so that it could be used for compost. Since human feces were n used for compost in America, Waksman suggested that Woodruff should study horse dung, hors