THE WAKSMAN INSTITUTE OF MICROBIOLOGY 1954 TO 1984

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Foreword

Except as otherwise indicated, this account of the history of the Waksman Institute is based on the author's personal recollections refreshed by perusing the reports of the Institute published by Rutgers, The State University of New Jersey, between 1955 and 1985. The first three reports were biennial, the others were published annually. In these reports, those interested will find complete lists of the personnel of the Institute and of the publications of the scientists associated with the Institute.

Figure 1. The Institute of Microbiology of Rutgers University shortly after its opening.

Introduction—Selman Abraham Waksman

The Waksman Institute of Microbiology of Rutgers University bears the name of its founder and his biographical sketch is an appropriate introduction to the history of this institution.

Selman Abraham Waksman was born of Jewish parents on July 22, 1888, in Novaya Priluka, a small town in the Ukraine. Although from an early age the child showed strong intellectual talents, these were not likely to be developed easily, as Tsarist Russia was rampant with anti-Semitism. In 1910, Selman left his homeland for the United States of

Figure 2. Dr. Selman A. Waksman, founder and first Director of the Institute.

America, where a cousin was a farmer in Metuchen, New Jersey. Selman had given some thought to the study of medicine but his cousin suggested that he seek guidance from Dr. Jacob G. Lipman, a professor at the Rutgers College of Agriculture and the Director of the New Jersey Agricultural Experiment Station.

Lipman recognized talent when he saw it and he convinced Waksman to enroll in the agricultural curriculum at the College. A New Jersey State scholarship provided needed financial support. Bright, highly motivated and hard-working, Selman put to good use his outstanding memory. He graduated in 1915, having been elected to Phi Beta Kappa.

Lipman put Waksman to work with his graduate students even before he had completed his undergraduate curriculum. His first research effort appeared modest but had a profound influence on the course of his whole scientific career. It was a study of the microbial population of soil profiles, recording the abundance and the kind of microorganisms that were present at various levels in the soil. He noted that, in addition to bacteria and fungi, his soil cultures contained microfungi or filamentous bacteria called actinomycetes, about which little was known. For the rest of his life, Selman maintained an interest in the actinomycetes, a group of organisms in which he soon became the world's foremost expert.

In 1916, having acquired a master's degree from Rutgers and and having married a young lady he had met in Russia, Waksman left for the University of California at Berkeley where he wrote a Ph.D. thesis under the direction of Dr. T. B. Robertson, a leading authority on the biochemistry of proteins. The Waksman marriage started on the wrong foot since Selman sat on his wife's new hat as the train departed for the west. However it weathered such setbacks and produced Dr. Byron Waksman, a distinguished immunologist named after one of Waksman's professors, Dr. Byron Halsted, for whom Selman worked part-time while a student at Rutgers.

Selman was industrious and always explored opportunities of scientific interest which might bring financial rewards. Thus, while in California working under Robertson on proteolytic enzymes of actinomycetes, Selman had a part-time position at Cutter Laboratories.

Upon graduation (1918) Waksman hesitated between a number of possibilities, but he decided to return to Rutgers to develop microbiology under the general supervision of Dr. Lipman. Here again, meager financial resources led to an industrial association as Dr. Waksman worked part-time on the antisyphilitic drug, Salvarsan, and on proteolytic enzymes at Takamine Laboratories in Clifton, New Jersey. Eventually, Dr.

Waksman devoted full time to his academic appointment and in 1930, he reached the rank of Professor. For the rest of his life, he remained a strong advocate of cooperation between the industry and the university (Waksman, 1954; 1958).

During Dr. Waksman's career, 77 students received advanced degrees for work done under his supervision; he wrote or edited 28 books and authored, alone or in collaboration, about 500 papers. The topics of his investigations were numerous and included the role of microorganisms in the decomposition of organic matter in soil, the development of humus, the production of enzymes, the formation and the utilization of peat, autotrophic bacteria, marine microbiology, thermophilic microorganisms, the role of heavy metals in the nutrition of fungi and the history of microbiology. From a practical point of view, his most important studies were those centered on microbial antagonisms and antibiotics, especially those produced by his first scientific love, the actinomycetes (Woodruff, 1968).

Over the years, a total of 18 antibiotics, mainly the products of actinomycetes, were isolated in Dr. Waksman's laboratory. Two of these, streptomycin and neomycin, have found extensive practical application and the bulk of the royalties received from the sales of these antibiotics were used to create and partially support the Institute of Microbiology which now bears the name of its founder. When the Institute opened its doors in 1954, two years after Dr. Waksman received the Nobel Prize for the discovery of streptomycin, Dr. Waksman was its first director. He retired in 1958 but maintained a laboratory at the Institute where work continued under his supervision on the biogenesis of streptomycin. After a few years he moved to New Haven, Connecticut, to be close to his son who was by then teaching at Yale University Medical School. On August 16, 1973, Dr. Selman A. Waksman died of a cerebral hemorrhage on Cape Cod, where the Waksmans had a summer home.

The Gestation Period

Dr. Jacob Lipman had wanted to create an institute of soil sciences on the campus of the College of Agriculture of Rutgers University. That dream never materialized, but the seed was sown in his disciple's mind. Many years later, when Selman A. Waksman was in a position to control large amounts of money, he revived and modified his mentor's ideas and created the Institute of Microbiology of Rutgers University. To understand this development, we should concentrate on one aspect of the soil studies of Dr. Waksman, namely his interest in the interactions of microbes in their natural environment, and realize that his industrial expe-

rience gave him the necessary background to exploit practical discoveries made in his laboratory.

In addition to his experience at Cutter and Takamine Laboratories, Waksman had been involved in the production of organic acids by fungi. A patent issued to him in 1943 for a process for the production of fumaric acids by *Rhizopus nigricans* was assigned half to Merck and Co. and half to Charles Pfizer and Co. Two other patents were issued in 1946 for the production of citric acid by strains of *Aspergillus* and were assigned to Merck and Co.

In 1938, Merck had retained Dr. Waksman as a consultant in the field of fermentation and supported work in his laboratory with an understanding that if some useful product(s) were to result from this work, Merck was to patent the invention and pay Rutgers University a royalty. As it turned out, the payoff did not come from the study of the production of organic acids by fungi but from Waksman's investigations of microbial interactions. As far back as 1923, Waksman and his close collaborator, Robert Starkey, wrote: "Certain actinomycetes produce substances toxic to bacteria, as shown . . . when around an actinomyces colony upon a plate, a zone is found free from fungus and bacterial growth."

In his posthumous book *The Antibiotic Era*, Waksman (1975) noted that the significance of these observations had escaped him, and little attention was paid to them in Waksman's laboratory until the discovery of tyrothricin by René Dubos, in 1939. Dubos was a former student of Waksman who was then working at the Hospital of the Rockefeller Institute for Medical Research. At the same time, Florey and Chain were reinvestigating the penicillin of Fleming, and the therapeutic potential of antibiotics became more obvious due to the chemotherapeutic success of the sulfa drugs. Waksman started an active program aimed at the detection, isolation, purification and characterization of antibiotics. The first discovery, actinomycin, was a toxic red pigment of a *Streptomyces* considered worthless until 1952, when C. Hackman, in Germany, reported its activity against Ehrlich carcinoma.

Success came in 1944 with the discovery of streptomycin, a *Streptomyces* aminoglycoside active against Gram-positive, Gram-negative bacteria and mycobacteria. It was effective against tuberculosis and brought the Nobel prize in physiology and medicine to Dr. Waksman in 1952, but it had its limitations. Prolonged treatment often resulted in ototoxicity and vestibular disturbances, in addition, bacteria became resistant to it. Neomycin, isolated in 1948, belonging to another class of aminoglycosides, did not allow easy development of resistance but nephrotoxicity and oto-

toxicity limited its use in humans mainly to topical applications and pre-surgical oral administration.

In 1939, Merck and Co. had made an agreement with Rutgers by which they were to support Dr. Waksman's work in the field of antimicrobial substances of microbial origin. Practical inventions were to be patented by Merck, which would pay Rutgers University a 2.5% royalty on sales of bulk products. Streptomycin was the first money maker and the royalties were paid to the Rutgers Endowment Foundation, later called the Rutgers Research and Educational Foundation. Merck gracefully agreed to transfer their rights to the Rutgers foundation, which licensed a number of manufacturers throughout the world. After some fumbling, the Rutgers foundation developed the pattern of returning 15% of the royalties received from the sale of a product to the inventors and of using the bulk of the income to build an endowment to support projects in the field of the invention (Lechevalier, 1980).

The Direction of the Institute

Monies coming from the sales of streptomycin became almost immediately available to the Department of Microbiology of the College of Agriculture of Rutgers University, which was headed by Dr. Waksman. A special allocation of $78,000 was used to build a virus research laboratory which was located behind Lipman Hall where the Department had moved in 1951.

As it became obvious that the royalties from streptomycin, soon to be fortified by the sales of neomycin, would represent several million dollars, Dr. Waksman started to think about strengthening general microbiology at Rutgers. At a meeting of the board of Trustees of the Foundation, held in July 1951, it was resolved that the Foundation should make available to the University $2,300,000 for the construction of a proposed Institute of Microbiology at University Heights, now called Busch Campus. Ground-breaking for the new building took place in September 1951. The cornerstone was laid in May 1952 and on June 7, 1954, the official dedication of the Institute took place. Professor Albert J. Kluyver of the Technical University of Delft, the Netherlands, was the main speaker. On this occasion, he received an honorary doctorate from Rutgers, as did Oswald T. Avery, George W. Beadle, Robert E. Buchanan, Richard E. Shope, Jacques Tréfouël, Hans K. von Euler-Chelpin and C. B. van Niel.

The Institute of Microbiology of Rutgers University, at its opening (Fig. 1) was an impressive 302-foot long Georgian Colonial style build-

ing overlooking the golf course of the University. It harbored 33,000 square feet of usable space which included a lecture hall seating 200 persons, a library with 7,000 volumes, a fermentation pilot plant with vessels ranging in size from five to 300 gallons, and such amenities, long since destroyed, as a dining room with a kitchen, a living room and a museum. The total cost of the project was about $3,500,000. When it opened, the new institute was staffed, in addition to its Director, Dr. S. A. Waksman (Fig. 2), by three Associate Professors, Drs. V. Groupé, virologist, W. J. Nickerson, microbial biochemist, Ruth E. Gordon, bacterial taxonomist, and two Assistant Professors, Drs. H. Lechevalier, microbiologist, and W. Szybalski, microbial geneticist. There were also six investigators with the rank of instructors. One of these, a chemist, Dr. C. P. Schaffner, is still a member of the Institute in 1988, as is H. Lechevalier. In addition, two distinguished retirees soon joined the Institute. These were Dr. Michael Heidelberger, immunologist, and Dr. Richard Kudo, protozoologist.

As early as 1949, in an article published in the journal *Science*, Dr. Waksman expressed his views on the aims and purpose of an Institute of Microbiology. First, he stated that microbiology was not receiving the recognition that it deserved as a branch of science. After defending microbiology and its achievements, Waksman indicated that the proposed Institute would emphasize research in six major fields: 1) general microbiology, 2) microbial physiology, 3) antibiotics, 4) vitamins and enzymes, 5) microbial ecology and 6) applied microbiology. In planning the program of the Institute, the broad field of microbiology was conceived by Waksman as covering the "six major groups of microorganisms: Bacteria, Actinomycetes, Fungi or Molds, Yeasts, Protozoa and Viruses." He also was ready to give minor consideration to such other groups as mushrooms, algae, certain worms such as nematodes and other microscopic forms of life.

Dr. Waksman remained the Director of the Institute during the first four years of its existence. During that period, the six fields of research listed above remained the official foci of activity of the Institute, in addition to graduate teaching and post-graduate training. One year after Dr. Waksman's retirement as Director, the building housing the Institute was named Waksman Hall. The naming of the Institute after him was accomplished only after his death.

When Dr. Waksman retired as the Director of the Institute, Dr. J. Oliver Lampen took the helm for the next 22 years. A native of Holland, Michigan, where he was born in 1918, Lampen received a Ph.D.

degree from the University of Wisconsin in 1943. At the time of his appointment at Rutgers, Dr. Lampen was Director of the Division of Biochemical Research at the Squibb Institute for Medical Research in New Brunswick, New Jersey. His early research dealt with the isolation of p-aminobenzoic acid as a growth factor for bacteria and led to the demonstration that the prevention of the formation of folic acid compounds from p-aminobenzoic acid was at the root of the mode of action of sulfonamides. For these fine investigations, he received the Eli Lilly Award of the American Society for Microbiology in 1952.

At Squibb, Lampen had already started a series of investigations on the mode of action of polyenic antifungal antibiotics. He and his colleagues demonstrated that these compounds acted by combining with sterols in the membranes, producing alterations which led to cellular loss of critical ions such as potassium and magnesium. Studies on polyenes were continued by Lampen at the Institute and enlarged to include griseofulvin, but soon he turned his attention to the mechanisms of formation and transport of extracellular enzymes. He investigated both a eucaryotic system (production of invertase by *Saccharomyces cerevisiae*), and a prokaryotic one (production of penicillinase by *Bacillus licheniformis*). In 1983, Lampen received the Rutgers Board of Trustees award for excellence in research.

In 1980, Lampen retired as the Director of the Institute but remained on the faculty and was able to devote his time to the direction of his own laboratory. Under the leadership of Dr. Lampen, the areas of research at the Institute were characterized as being a) synthesis and function of microbial products, b) immunology and virology with emphasis on cancer, and c) molecular genetics and cellular regulation, and the Institute was enlarged by the construction (1964) of an animal building which provided 4,000 square feet of animal quarters and specialized laboratories, including a suite of isolated rooms for work with pathogenic organisms.

Following Dr. Lampen's retirement as Director, the leadership of the Institute was passed to Dr. David Pramer (Fig. 3), a microbial ecologist. Pramer was born in Mouth Vernon, New York in 1923 and, working under the direction of Dr. R. L. Starkey on the fate and effect of streptomycin in soil, he received a Ph.D. degree from Rutgers University in 1952. After postdoctoral studies in England, he returned to the Department of Microbiology of the College of Agriculture of Rutgers University, in 1954. Upon Dr. Starkey's retirement in 1965, he took over the chairmanship of that Department. He left in 1969 to concentrate his efforts on administrative ventures that culminated with the Directorship of the Waksman Institute of Microbiology in 1980.

Figure 3. Dr. J. O. Lampen (right), second Director of the Institute with Dr. David Pramer, the third Director (left).

Pramer's research dealt with the fate of antibiotics in soil and plants, with marine microbiology, the decomposition of herbicides and pesticides in soil, and the nematode-trapping fungi. Under Pramer's direction, the areas of specialization of the research at the Institute were expressed as being: 1) Synthesis and function of metabolic products of microorganisms and other cells of commercial and medical value; and 2) Molecular genetics and cellular regulation. Pramer added continuing education as a regular activity of the Institute. He received the Rutgers President's award for Public Service in 1985.

Pramer inherited an expansion program initiated under Dr. Lampen's directorship, namely the building of an annex to Waksman Hall providing 20,000 square feet of laboratories and support facilities to be dedicated to a Center for Molecular Genetics. This building was completed in 1985.

While the building of the annex was in progress, a search was made for a person who would direct the further development of molecular biology at the Intitute. Eventually, the idea of a separate center was dropped and Dr. Joachim Messing was selected not only to direct the development

of molecular biology at the Institute but also to coordinate all efforts in this field at Rutgers. He received the title of Research Director of the Waksman Institute. Dr. Messing received his doctoral degree from the University of Munich, Germany, in 1975 and was Professor of Biochemistry at the University of Minnesota at the time of his appointment at Rutgers. Having developed phage M13 as a cloning vector, he turned his research interest to the regulation of gene expression in higher plants. His appointment was followed by the addition of plant growing facilities to the Waksman Institute.

In 1983, while the Institute was being enlarged, the New Jersey Commission on Science and Technology initiated the development of a Center for Advanced Biotechnology and Medicine (CABM) to be built in Piscataway, New Jersey, between the Waksman Institute and the Robert Wood Johnson Medical School. The CABM will be linked by covered passages to the two previously mentioned institutions. As part of the CABM, a state-of-the-art cell and cell product facility is being completed at the Institute and one of the floors of the Institute's annex is being used temporarily by the CABM in order to permit its Director, Dr. Aaron Shatkin, to assemble a nucleus of investigators. The Waksman Institute will thus become part of an extensive biomedical and biotechnical complex.

During the first 30 years of its existence, the Institute, as we have seen, had three Directors. Three faculty members, Drs. V. Bryson, Sewell Champe and H. Lechevalier served at times as Associate Directors, and in the Director's absence, as Acting Directors. In the administrative aspects of running the Institute, the Directors received the support of an Executive Secretary or Associate Director for Administration. Two persons served in this capacity: Mr. Edward Isaacs, from 1953 to 1979, and Mrs. Shirley Brown, from 1979 to the writing of this paper (1988).

Mr. Edward Isaacs was born in Westfield, New Jersey in 1917, and received a B.A. degree from Rutgers University in 1939. He was aiming for a career as a journalist but the war found him in the Air Force as an intelligence officer. After a few years working for the Rutgers University Public Relations Department, he assisted Dr. Waksman in establishing the Institute and helped Dr. Lampen run it. Extremely active in civic activities, Ed Isaacs held, among other posts, the Chairmanship of the Board of Trustees of St. Peter's Medical Center in New Brunswick, New Jersey, and played an important role in the improvement of health care delivery in New Jersey. Following his retirement in 1979, he moved to Boca Raton, Florida, where he died in 1985.

Shirley Brown is a native of Philadelphia who received both B.A. and M.A. degrees from Temple University. After teaching chemistry and mathematics at Upsala College in New Jersey, she joined Rutgers University's administration as an academic planner in 1974, and replaced Ed Isaacs upon his retirement.

Antibiotics, Other Microbial Products, and Microbial Taxonomy

Although Dr. Waksman wanted the research at the Institute of Microbiology to cover many different aspects of this science, the Institute was the fruit of his interest in actinomycetes and their antibiotics, and for many years the general perception remained that antibiotics constituted the main field of research at the Institute.

Two of the faculty members who were at the Institute in its early days and who continued distinguished careers at other institutions in the field of antibiotics and microbial products are Dr. Leo Vining and Dr. Edward Katz.

Vining was a native of New Zealand who obtained his Doctorate in chemistry from Cambridge University. After postdoctoral training at the University of Kiel with Dr. H. Brockmann, he joined Dr. Waksman's Department in 1953 and left in 1955 for Canada, where he developed a brilliant career. He received numerous prizes, including the Charles Thom Award of the Society for Industrial Microbiology.

Ed Katz received a Ph.D. degree from Rutgers (1951) while working under Dr. Waksman. After three years at the University of New Hampshire, he joined the faculty of the Institute where he started to work on actinomycins, which had become popular because of their antitumor activity. In 1960 he left for the National Institutes of Health and eventually became a professor at Georgetown University Medical School. His research has been concerned with the biochemistry and genetics of the synthesis of the actinomycins, a subject in which he is the world's foremost expert.

Table 1 gives the list of the antibiotics which were isolated at Rutgers University. The 10 antibiotics isolated after the opening of the Institute were the results of studies carried out in three different laboratories, those of Carl Schaffner, Hubert Lechevalier and Lloyd McDaniel. None of these antibiotics have found practical applications.

Carl P. Schaffner worked on antibiotics of streptomycetes under the supervision of Dr. H. E. Carter at the University of Illinois, and received a Ph.D. degree from that institution in 1953. Upon graduation, he joined Dr. Waksman's Department at the College of Agriculture.

TABLE I

ANTIBIOTICS ISOLATED AT RUTGERS UNIVERSITY

Actinomycin	Chromooligopeptide	Waksman and Woodruff (1940)
Streptothricin	Peptidoaminoglycoimidazole-piperidone	Waksman and Woodruff (1942)
Clavacin (patulin)	Lactone	Waksman *et al.* (1942)
Fumigacin (helvolic acid)	Steroid	Waksman *et al.* (1942)
Streptomycin	Aminoglycoside	Schatz *et al.* (1942)
Chetomin	Neutral sulfur-containing substance	Waksman and Bugie (1944)
Micromonosporin	Anthracycline	Waksman *et al.* (1947)
Grisein	Sideromycin	Reynolds *et al.* (1947)
Streptocin	Acid with antiprotozoal activity	Waksman *et al.* (1949)
Neomycin	Aminoglycoside	Waksman and Lechevalier (1949)
Fradicin	Weak base	Swart *et al.* (1950)
Rhodomycetin	pH indicator	Shockman and Waksman (1951)
Ehrlichin	Large molecule	Groupé *et al.* (1951)
Viscosin	Lipoglucocyloligopeptide	Kochi *et al.* (1951)
Antimycoin	Tetraene	Raubitschek *et al.* (1952)
Candicidin	Heptaene	Lechevalier *et al.* (1953)
Candidin	Heptaene	Taber *et al.* (1954)
Mycothricin	Peptidoaminoglycoimidazole-piperidone	Schaffner *et al.* (1956)

3′-Amino-3′-deoxyadenosine		Gerber and Lechevalier (1962)
1,6-Phenazinediol-5-oxide		Gerber and Lechevalier (1965)
5,8-Dihydroxy-2,7-dimethoxy-1,4-naphthoquinone		Gerber and Wieclawek (1966)
1,6-Dimethoxyphenazine; 6-methoxy-1-phenazine		Gerber (1967)
Nonyl, cyclononyl and cyclomethyldecylprodiginine		Gerber (1971)
Candihexin	Hexaene	Martin and McDaniel (1974)
Butylcycloheptylprodiginine		Gerber and Lechevalier (1976)
Hydroheptin	Heptaene	Tunac *et al.* (1979)
Peniophorynes	Polyacetylenes	Gerber *et al.* (1980)

Reference to the papers listed in this table can be found in Lechevalier, 1982.

Schaffner's studies have centered on the separation of water-soluble antibiotics of the aminoglycoside type and on the polyenic antifungal antibiotics. He also investigated microbial transformations of steroids. In addition to numerous studies on the chemical structure of antifungal polyenes, Schaffner and his co-workers introduced several chemical derivatives of these substances, having reduced toxicity while retaining antifungal activity. He has been concerned with the other biological activities of the polyenes, such as their role in the reduction of the size of prostates and other aspects of their effect in lipid metabolism. Other groups of antibiotics studied in Schaffner's laboratory have included anthracyclinones and isochromanequinones. Recently, he has been concerned with the antiviral activity of polyenic derivatives.

Hubert Lechevalier was a native of France who came to Canada as a child. He received an M.S. degree from Laval University in 1948 for a study of the use of antibiotics from gram-negative bacteria in the treatment of Dutch elm disease. He sought further training in the field of antibiotics under the supervision of Dr. Waksman and he received a Ph.D. degree from Rutgers University in 1951. Soon after his arrival at Rutgers, Lechevalier isolated two strains of *Streptomyces* that were to keep him and many other people in academia and industry busy for several years. These were the *S. fradiae* producer of neomycin and the *S. griseus* elaborating candicidin. Both of these antibiotics were of practical value, and neomycin added substantially to the funds available to the Institute of Microbiology. Lechevalier's work and that of his two major associates Dr. Nancy N. Gerber and Mary P. Lechevalier has been mainly concerned with actinomycetes and their products. He received the Lindback Award for distinguished research in 1976.

Mary P. Lechevalier came to Rutgers in 1949 for graduate training under Dr. Waksman. She received an M.S. degree in 1951 for a study of antiviral antibiotics. After a stage as an industrial microbiologist at E. R. Squibb and Sons she joined her husband at the Institute. An excellent microscopist, she has isolated numerous novel forms of actinomycetes and developed a system of taxonomy of actinomycetes which is based on their morphology and on their chemical composition, namely cell wall, whole cell sugar, and lipid composition. For this work she received jointly with her husband the Charles Thom Award of the Society for Industrial Microbiology in 1982. Recently, she has been mainly interested in a group of nitrogen-fixing actinomycetes belonging to the genus *Frankia*.

Nancy N. Gerber (1929-1985) worked with Dr. R. A. Barnes at Rut-

gers University on the chemistry of the antifungal agent of osage orange wood and was awarded a Ph.D. in chemistry in 1957. After three years as an industrial chemist, she joined Lechevalier's laboratory at the Institute where she remained until her death. Surrounded by microbiologists, she determined the structures of the compounds that they found and often elucidated their biosynthetic pathways. She worked on aminonucleosides, phenazines, phenoxazinones, naphthoquinones, prodiginines, sugars, sesquiterpinoids, lactones, and polyacetylenes. She found that strains of *Frankia* produce benzonaphthacene quinones with ring systems previously unknown among natural products. She was a specialist of microbial pigments and of volatile substances that impart characteristic odors to soil and water bodies.

Hubert Lechevalier and his co-workers touched on a number of other points. They developed various screening methods, studied the distribution of diverse types of actinomycetes in soils and water bodies, including waste water treatment plants, investigated the nutritional requirements of actinomycetes, characterized respiratory pigments of actinomycetes, demonstrated cross-resistance between silver-containing compounds and antibiotics, studied the morphogenesis of sporulating and resting structures of actinomycetes, studied the removal of heavy metals from waste waters by microbial biomasses and proteins and isolated restriction endonucleases from strains of *Micromonospora*.

When Dr. Waksman planned the Institute of Microbiology, high on his list of priorities was the installation of a pilot plant for the production of microbial cells or microbial products needed by the investigators of the Institute. An old friend of Dr. Waksman, Dr. Adolph Zimmerli, volunteered to design the plant. Dr. Zimmerli (1886-1967) was a native of Switzerland and a graduate in chemical engineering of the Swiss Federal Institute of Technology in Zurich. After working in France, he emigrated to the United States where he became a consulting engineer.

In 1961, Dr. Lloyd E. McDaniel relieved Dr. Zimmerli of most of the pressure of supervising the pilot plant. McDaniel was a product of Dr. Elizabeth McCoy's laboratory at the University of Wisconsin, where he investigated the production of butyl alcool and received a Ph.D. degree in 1941. After spending 20 years at Merck and Co, McDaniel started his academic career at the Institute. He retired in 1984. McDaniel and his collaborators studied oxygen transfer in shake flasks, determining the type of baffling, flask closures and speed of rotation in shaking machines that would give results comparable to those obtained in reactor vessels. In his work, McDaniel concentrated on polyenic antifungal an-

tibiotics; he and his collaborators determined that the aromatic ring in candicidin and similar antibiotics originate directly from p-aminobenzoic acid and that phosphate stimulates the growth of the producing organisms but inhibits the production of the polyenes.

While the Lechevaliers, as we have noted, were deeply involved in taxonomic studies, the "official" taxonomist of the Institute was Dr. Ruth E. Gordon. She received a Ph.D. in 1934 from Cornell University where she developed a lasting interest in mycobacteria and in nocardiae. In 1939, Gordon obtained a position at the Department of Agriculture where she soon developed expertise in the bacteria of the genus *Bacillus*. From 1944 to 1950, she worked at the American Type Culture Collection (A.T.C.C.). She was Curator of the whole collection when she joined Dr. Waksman's Department at the College of Agriculture. Dr. Gordon took care of the Institute's collection, which was terminated with her retirement in 1981. By that time, she was a world-renown authority on the taxonomy of the bacilli, the fast-growing mycobacteria and the nocardiae. She returned to the Washington area as a visiting investigator at the A.T.C.C. For her outstanding contributions to culture collections and taxonomy, she received the J. Roger Porter Award of the U.S. Federation of Culture Collections in 1983.

Biochemistry

We have already mentioned the extensive biochemical studies of Dr. J. O. Lampen and his associates, but the dean of the Institute's microbial biochemists was Dr. Walter J. Nickerson (1915-1979). He studied under Dr. Kenneth V. Thimann at Harvard University, from which he received a Ph.D. degree in 1942. After teaching at Wheaton College in Massachusetts, he joined the Air Force, where he carried out research in aviation physiology. As a Guggenheim Fellow he received postdoctoral training at the Carlsberg Brewery Laboratories in Denmark and at the Technical University of Delft in the Netherlands. Upon his return, he held appointments at Tufts Medical School, Brown University, and Wheaton College, where he taught botany and bacteriology.

Nickerson's early investigations of the biochemical control mechanisms of morphogenesis in fungi, the nutrition and physiology of pathogenic fungi and his knowledge of yeasts attracted the attention of Dr. Waksman, who asked him to join the faculty of his Department at the College of Agriculture in 1950. Nickerson and his associates were involved in many aspects of general and applied microbial biochemistry. His work centered on the study of macromolecules with emphasis on the structure and com-

position of the yeast cell wall and the factors controlling morphogenesis in fungi, especially their dimorphism. He was also deeply interested in photochemistry and in the degradation of complex polymers. In this last field, he studied in turn the degradation of keratin, citrus fruit rinds and rubber. These studies had commercial and ecological implications. A keratinase found in his laboratory to be produced by *Streptomyces fradiae* was for a short period of time on the market for use in the manufacture of leather. In addition, Nickerson and his co-workers contributed to medical microbiology by developing a chemically defined medium for the production of chlamydospores by *Candida albicans* and a diagnostic medium for the same fungus.

Biochemistry at the Institute was fortified with the appointment of Dr. Henry J. Vogel in 1957. He was born in Germany and had received a Ph.D. degree from New York University in 1949. He left the Institute in 1968, having accepted a position in the Department of Pathology at Columbia University's College of Physicians and Surgeons. Dr. Vogel and his associates were concerned with the pathways of amino acid formation and with comparative biosynthesis, with interest in changes in pathways during the course of evolution, and in enzyme biogenesis, with special attention to induction and repression of enzyme formation. The biosynthetic pathways of the basic amino acids ornithine, lysine and arginine were the main subjects of these studies in which biochemical, genetic and biomolecular approaches were used. Dr. Vogel received a Lindback award in 1966 for excellence in research and teaching.

Dr. Lampen's laboratory contributed further to the development of microbial biochemistry by acting as an incubator from which two independent investigators were added to the Institute's faculty. The first one was Dr. Bijan Ghosh, who had received a doctorate in physiology from the University of Calcutta in 1963. After postdoctoral training in electron microscopy at the University of Western Ontario with Dr. R.E.G. Murray, he joined Dr. Lampen's group in 1967. Eventually he took charge of the Institute's electron microscopy laboratory previously supervised by H. A. Lechevalier. Dr. Ghosh concentrated on the localization of enzymes in situ and quantitative electron microscopic methods. He left in 1973 for the Department of Physiology of the Robert Wood Johnson Medical School.

In 1971, Jan S. Tkacz received a Ph.D. degree from Rutgers University for work done under the supervision of Dr. Lampen. After postdoctoral training at Harvard Medical School and the Hershey Medical Center in Pennsylvania, he returned to the Institute in 1975 and remained

until 1981 when he joined the research laboratories of E. R. Squibb and Sons. While at the Institute, Tkacz worked on protein glycosylation, its role in the folding of polypeptides into enzymatically active configurations, and the export of glycoproteins. In this process, he elucidated the mechanism of action of tunicamycin, an antibiotic inhibiting protein glycosylation.

Genetics and Molecular Biology

In the field of genetics, Dr. Waksman understandably wished to emphasize the actinomycetes. The person he first selected in this field in 1954, Dr. Waclaw Szybalski, investigated with his associates the exchange of nuclear material in strains of *Streptomyces*. However, Szybalski did not limit his studies to the actinomycetes but also investigated the mechanisms of mutagenesis in bacteria and the replication of phages. Szybalski was born in Poland and received a doctorate from the Gdansk Polytechnical Institute in 1949. Before joining the Institute, he had received industrial experience at Wyeth Laboratories, in Pennsylvania, and had had contact with the best geneticists of the time at Cold Spring Harbor Laboratories. Szybalski left for the University of Wisconsin in 1960.

Another versatile addition to the Institute faculty was Vernon Bryson (1913-1985), who received a Ph.D. degree from Columbia University in 1944. He became a microbial geneticist while at the Carnegie Institute's laboratories at Cold Spring Harbor, where he was located from 1942 to 1955. Following a year as a program director at the National Science Foundation in Washington, D.C., he responded to Waksman's appeal and joined the Institute in 1956, remaining until 1976 when he left for Cook College (a new name for the College of Agriculture) where he devoted himself to teaching. Bryson had many interests, including the study of microbial resistance to drugs and radiation and the development of turbidistats where bacterial populations could be maintained at a constant state, but most of his work at the Institute was centered around the study of mutations in enterobacteria, especially the study of mutator genes.

A bright young star was added to the faculty of the Institute with the appointment of Ekkehard K. F. Bautz. He had received a Ph.D. degree from the University of Wisconsin in 1961 and, after a postdoctoral stay at the University of Illinois, joined the Institute in 1963. He was deeply involved in the molecular biology of messenger RNA and phage T4. Bautz' greatest achievement at the Institute was the discovery of the sigma factor of RNA polymerase which is required for promoter binding. In 1971 Bautz left for the University of Heidelberg, in his native Germany.

Dr. Sewell P. Champe joined the faculty of the Institute in 1969. Having received a Ph.D. degree from Purdue University in 1959, Champe was well known to molecular biologists for his discovery of nonsence mutations. At the Institute, his work was involved until 1977 with the morphogenesis of phage T4, more specifically with the nature, origin, fate and role of a set of small polypeptides, of unusual composition, which are encapsulated with the DNA in the head of T4. In the late 1970's he shifted his attention to the genetic control of morphogenesis in *Aspergillus nidulans*, with concentration on the genes that initiate sporulation. This led to the discovery of a metabolite with hormone-like activity that stimulates sexual sporulation.

With the arrival of Dr. David H. L. Bishop in 1971, one of the laboratories of the Institute was devoted to the transcription of RNA animal viruses. Bishop was a native of London who received a doctorate from the University of Liverpool in 1962. He was at Columbia University when he was appointed at the Institute. In 1975, he left for the University of Alabama Medical Center in Birmingham. His work was concerned with rhabdoviruses, especially their RNA-directed polymerases. Much of this work was carried on the vesicular stomatitis virus.

Another later addition to the faculty was Dr. Vivian L. MacKay, who studied the mating regulatory system of the yeast *Saccharomyces cerevisiae*. MacKay received a Ph.D. from Western Reserve in 1972 and after a postdoctoral stay at the University of California at Berkeley, she joined the Institute in 1974, and left for ZymoGenetics, in Seattle, in 1982. Most of the work of MacKay and her associates was concerned with the genes required for conjugation in *S. cerevisiae*. In that yeast, diffusible peptide mating hormones are needed for the conjugation of compatible haploid cells.

When Dr. V. Bryson decided to move to Cook College, one of the members of the Cook faculty, Dr. Carl A. Price, who had been teaching there since 1959, was interested in spending more time on research and moved to the Institute in 1976. Price received a Ph.D. degree from Harvard University in 1952 and came to Rutgers after having received postdoctoral training at Harvard, Sheffield and Purdue Universities. An expert on photosynthesis and plastids, Price is mainly known for the development of procedures for the isolation of subcellular components and, consequently, his profound knowledge of centrifugation techniques.

When Dr. B. Ghosh left the Institute in 1973, the supervision of the electron microscopic (EM) unit was somewhat "haphazard" until Dr. Lee D. Simon was appointed at the Institute, in 1976. Simon received a

Ph.D. degree from the University of Rochester in 1966 and was at the Institute for Cancer Research in Philadelphia at the time of his appointment to the Institute. In addition to being a top-notch electron microscopist who greatly improved the Institute's EM unit, Simon has been concerned with the mechanism of adsorption of T-even phages to bacterial cells and with the breakdown of proteins within bacterial cells.

Dr. Navin K. Sinha's research has been concerned with the mechanism of DNA replication, especially with the fidelity of this replication. A native of India, he received a Ph.D. degree from the University of Minnesota in 1972 and, after postdoctoral training at MIT and at Princeton University, he joined the Institute in 1976.

With the appointment of Dr. William H. Sofer a collection of fruit flies joined the microorganisms of the Institute. Sofer received a Ph.D. from the University of Miami in 1967. The rest of his career was spent at Johns Hopkins until he moved to the Institute in 1980. Sofer and his co-workers study the control of the gene of alcohol dehydrogenase in *Drosophila melanogaster*. Two important findings have come out of his laboratory: a chemical selection scheme for the detection of flies which lack alcohol dehydogenase activity, and a technique of somatic transformation consisting of injecting genes into fly embryos and having them expressed in the larval and adult stages.

The Institute was strengthened in the field of genetics and molecular biology in 1983, when three groups of investigators arrived from Douglass College. One of these was headed by Dr. Evelyn Witkin. Witkin received a Ph.D. degree from Columbia University in 1947, having worked with such luminaries as T. Dobzhansky and S. E. Luria. She held positions in the Department of Genetics of the Cold Spring Harbor Laboratories and at the Downstate Medical Center of the State University of New York. In 1955 she became a Professor at Rutgers and was located at Douglass College until her move to the Institute. Witkin, a member of the National Academy of Sciences, is well known for her work on the repair of DNA which has been damaged by radiation. An exception in our modern world of "research by squads", Witkin has done most of her research herself. She has had few graduate students and after 40 years of research she has not yet guided a postdoctoral fellow.

The basic problem in cancer is why, under apparently the same conditions, tumor cells continue to divide while normal cells know when to stop. This problem is the focus of the research carried out by a group headed by Dr. David Axelrod, who also arrived from Douglass College in 1983. Axelrod received a Ph.D. degree from the University of Ten-

nessee (1967). After spending two years as a postdoctoral fellow at the Albert Einstein College of Medicine, he joined the faculty of Rutgers University at Douglass College in 1970. In his work, Axelrod uses mouse fibroblast cells transformed by the *ras* oncogene from human bladder tumor cells. He tries to identify new genes that suppress the expression of the *ras* oncogene.

The last of the Douglass emigrants, Dr. Warren Maltzman, also worked on cancer; he received a Ph.D. degree from the University of California at Berkeley in 1977. After three years postdoctoral training with Dr. A. J. Levine at Princeton and Stony Brook, he was appointed at Rutgers. His research, aimed at gaining insight into neoplastic cellular growth, focused on attempting to elucidate the role of a cellular protein antigen, p53, which is expressed at increased levels in rapidly growing cells, including some neoplastically-transformed mammalian cells.

Immunology

One year after the Institute opened, Dr. Michael Heidelberger, who had just retired from Columbia University's College of Physicians and Surgeons in New York City, joined the Institute as an Honorary Professor of Immunochemistry. His disciple, Dr. Otto Plescia, came with him. Dr. Heidelberger, one of the most distinguished immunologists in the world, was already at that time a member of the National Academy of Sciences and had received numerous honors. While he was at the Institute, he continued his studies of polysaccharides of pneumococci and of polysaccharides which cross-react with the pneumococcal antibodies. These studies of the chemical structure of polysaccharides were based on immunological reactions mainly developed by Heidelberger during his long and fruitful career. He left the Institute in 1964 to join the Department of Pathology of the New York University School of Medicine where he still has a laboratory at age 100.

Plescia received a Ph.D. in chemistry from Cornell University in 1947. He was associated with Dr. Heidelberger at Columbia University and was a natural choice to help him develop immunology at the Institute. At that time, Plescia's main interest was the chemical nature of the various components of complement. The aim of these studies was to understand the mechanism of complement fixation and the mode of action of complement in immune hemolysis.

As Drs. Heidelberger and Plescia were moving in the newly opened Institute, in 1955, Dr. Werner Braun (1914-1972) was appointed Professor of Bacteriology. Dr. Braun was born in Germany and was a recognized authority on bacterial genetics and medical bacteriology. He was

especially interested in brucellae and in factors that affect changes in the virulence of bacterial populations. Brucellae were the center of an active program from 1957 to 1960 when Dr. Warren Stinebring was at the Institute. He continued work in this field at the University of Pittsburgh and at the University of Vermont.

Meanwhile, Braun's scientific interest shifted with time to problems of cellular resistance and he and Plescia became close collaborators. One of the most outstanding discoveries of the Plescia-Braun team was that DNA, partially degraded by enzymatic action, changed avirulent brucellae to virulent ones. These DNA-DNAse preparations also increased antibody formation. Also of importance was the discovery that nucleic acids were antigens if complexed with methylated bovine serum albumin, and that polymers of synthetic polynucleotides, such as poly A, poly U etc., stimulated antibody formation in several test systems including experimental tumors. The mode of action of synthetic polynucleotides was explored and revealed the enhancing effect of cyclic AMP and theophylline. Further it was found that prostaglandins had a modulating effect on the release of cAMP.

When death interrupted the fruitful cooperation between Braun and Plescia, the latter continued the studies of the factors which influence immunoregulation. Plescia came to the conclusion that metabolites of arachidonic acid, produced during antigenic stimulation, play an important role in regulating the immune response and has turned most of his attention to the possible role of these metabolites in contributing to the immunodeficiencies of patients with cancer and AIDS, two major plagues of our times.

In 1969, Dr. Arthur Gottlieb, who had received an MD degree from New York University in 1961, and who was at Harvard University Medical School, joined the Institute. His research interest was the molecular biology of antibody-forming systems, especially the biology of lymphoid systems. The most important aspect of his research was the study of the chemical nature of the "transfer factor". This factor, found in extracts of human peripheral leucocytes, transfers delayed hypersensitivity from donors, sensitive to various antigens, to negative recipients and it had been found capable of correcting states of cell-mediated immunodeficiency. When Professor Gottlieb left the Institute in 1975 to become the Chairman of the Department of Microbiology and Immunology at Tulane Medical School, he and his associates had demonstrated that the "transfer factor" phenomenon in humans was not mediated by double-stranded RNA.

For a short period of time, one of the laboratories of the Institute con-

centrated exclusively on tumor immunology. In 1978, Dr. Kiu Leung joined the Institute. His work involved, among other things, the development of monoclonal antibodies to tumor-associated antigens of a sarcoma induced by methylcholanthrene. Leung left in 1982 to continue his research at the Department of Medical Microbiology and Immunology of Ohio State University.

Virology

Dr. Waksman considered virology an important part of microbiology and no doubt was mainly interested in the development of antiviral agents. However, he also understood the value of gaining fundamental knowledge in this field.

Dr. Vincent Groupé joined Dr. Waksman's Department in 1949 and, as previously mentioned, a small building was erected in back of Lipman Hall to house the virus research laboratory which was his domain. Vince, as he was known to his friends, received a Ph.D. from the University of Pennsylvania in 1942. After graduation, he worked for five years at E.R. Squibb and Sons, and after two years at the Experiment station of the University of Connecticut, he joined Dr. Waksman's operation. In 1968, he left to go to Life Sciences, Inc., in St. Petersburg, Florida.

The investigations of Dr. Groupé, his students and associates involved the discovery of an antiviral agent, Ehrlichin (Table 1), but mainly centered on the biology of tumor causing viruses. He worked with many avian and murine systems but the bulk of his work was with the Rous sarcoma virus. Another interesting discovery of Groupé's laboratory was xerosin, an antiinflammatory agent from a bacterium which remained an object of studies for many years. One of Dr. Groupé's students, Frank Rauscher, soon became famous for his isolation of the murine leukemia virus that bears his name. Eventually Rauscher became the Director of the Cancer Institute of the National Institutes of Health. Another student of Dr. Groupé, Robert W. Simpson, who had received a Ph.D. from Rutgers in 1958, returned to the Institute after 10 years at the Department of Virology of the Public Health Service Institute of New York.

Before Simpson joined the Institute, his investigations had centered on the genetics of the virus of influenza and the biochemistry and genetics of a rhabdovirus, the vesicular stomatitis virus and he continued these investigations with his associates at the Intitute. Soon, the rather important discovery of an RNA-dependent RNA polymerase in influenza virions was made in his laboratory. This was the first demonstration that a human respiratory virus carried its own transcriptase enzyme necessary for ini-

tiating viral RNA synthesis in infected cells. Current research on viral chemotherapy includes attempts to develop drugs that will inhibit the influenza transcriptase. However, the main thrust of the research with influenza and other respiratory viruses was the development of conditional-lethal temperature-dependent mutants that could be used as safe live vaccines. The Simpson group has also worked on many other viruses, usually causing respiratory diseases. In some investigations, they used strains of coronaviruses which had been isolated previously by Dr. Fred Beaudette of Rutgers, an old friend of Dr. Waksman and a recognized authority on avian viruses.

Another significant discovery of Simpson and his co-workers was that of a parvovirus associated with rheumatoid arthritis patients. This virus causes various disorders in mice including swelling and deformations of their articulations. It was found to be most closely related to the bovine parvovirus. The full medical implications of these viruses are presently under investigation.

With the appointment of Dr. Karl Maramorosch as Professor, the Institute acquired a versatile scientist who among his fields of expertise included insect and plant viruses. Born in Vienna, Austria, Maramorosch received a master's degree from the Technical University of Warsaw in 1938 and a Ph.D. degree in plant pathology from Columbia University in 1949. In 1974, he left the Boyce Thompson Institute of Plant Research to join the Institute's faculty. He and his associates worked on insect viruses, the development of arthropod and invertebrate tissue culture systems to grow viruses, intracellular bacterial plant pathogens, especially mycoplasmas, biological methods of control of insect pests, and recently his interest has expanded to the development of vaccines against protozoal diseases such as malaria and babesiosis. Maramorosch received the 1980 Wolf Prize in Agriculture for his many accomplishments and especially for his indefatigable efforts at improving world agriculture.

Conclusion

The duties of the members of Institute, as Dr. Waksman saw them, were to carry out research in one of the many branches of microbiology, to participate in teaching in graduate courses, and to guide graduate students and postdoctoral fellows. Dr. Waksman saw the Institute as a center of learning which would also attract visiting investigators and where research and teaching would be carried out in a relaxed atmosphere esthetically pleasing and free of financial worry.

Reflecting upon the first three decades of existence of the Waksman

Institute, one can ask if the wishes and the dreams of its founder have been fulfilled. Dr. Waksman wanted an Institute of Microbiology in which, as we have seen, many different aspects of microbiology would be investigated. The diversity that Waksman aimed for was never achieved, but the diversity of the intellectual production is still impressive.

If one examines the journal publication output of the 14 laboratories that were functional during the first two years of the Institute's existence, we note the following distribution in topics covered:

Subject	*Number of papers*
antibiotics and fermentations	24
virology	9
biochemistry	8
genetics and molecular biology	5
history and general discussions	5
taxonomy	3
immunology	1

During the 29th and the 30th years, 17 laboratories published papers as follows:

Subject	*Number of papers*
genetics and molecular biology	37
antibiotics and fermentations	12
taxonomy	8
parasitology	8
history and general discussions	8
virology	7
biochemistry	7
agriculture	4
immunology	1

The obvious conclusion to be drawn from this sampling is that genetics and molecular biology have replaced antibiotics as the major field of study at the Institute. Dr. Waksman would not have objected to this, but he would have preferred to see these molecular genetic studies directed to the production of antibiotics by actinomycetes rather than involved in a multitude of seemingly unrelated subjects.

The Institute has been, during these thirty years, a center of learning which has attracted scientists from many lands. It has harbored numerous

seminars, lectures, workshops and symposia. The most important of these was the Third International Fermentation Symposium held in 1968. Some of these lectures and symposia have been published as books and were sponsored by pharmaceutical and/or chemical manufacturers.

Many of the amenities of the original building have given way to the pressures of functionality: the museum became a laboratory, then a reception room; the kitchen, a fruit fly room; the dining room, a classroom; locker rooms have been eliminated; the number of washrooms has been reduced.

The endowment of the Institute has provided some financial support to the members of the Institute, although it never reached the level that Dr. Waksman wished. However help came from another quarter in the form of the Charles and Johanna Busch bequest, which was received by the University in 1971 in part to help support the Institute.

One may argue at present that the Waksman Institute of Microbiology no longer focuses primarily on microbiology. Foci of interest will change as science evolves and, as the house of Pasteur is called L'Institut Pasteur, it is probably best to refer to the house of Waksman simply as the Waksman Institute.

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