THE ROAD TO STREPTOMYCIN AND BEYOND. A CHAPTER IN THE HISTORY AND APPLICATION OF ANTIBIOTICS

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SEARCH FOR ANTIBIOTICS

Antibiotics are produced by microorganisms which inhabit the soil and are found also in the dust and other natural substrates. The search for organisms capable of producing antibiotics was begun in my laboratories at the New Jersey Agricultural Experiment Station in 1936. It was preceded by more than two decades of study of fungi, actinomycetes and bacteria, largely inhabiting soils, composts and peat bogs. These studies culminated in the isolation, in 1940, in crystalline form, of actinomycin produced by an actinomycete culture. Gradually we limited ourselves to the actinomycetes, a group of higher, filamentous bacteria that form a large part of the microbial soil population.

Actinomycin proved to be too toxic to the animal body. Assisted by an every growing group of graduate students and visiting investigators, I continued these investigations. They resulted in the isolation of other compounds possessing antimicrobial properties. In 1942, we isolated, from another actinomycete culture, streptothricin. This antibiotic was active upon a large number of gram positive and gram negative bacteria, as well as upon certain fungi. It was water soluble and heat stable. Unfortunately, although much less toxic than actinomycin, it displayed a certain, toxicity in experimental animals.

We were now led to search for a type of antibiotic that would be similar in its chemical and biological properties to streptothricin, but without the delayed toxic effect upon animal cells. Late en 1943, we isolated such an antibiotic, which we named streptomycin. This name was derived from the newly created generic name of the group, *Streptomyces.* This name was established for the genus only a few months earlier by myself and the late Dr. Arthur T. Henrici for the group of sporulating, aerial mycelium producing actinomycetes found predominantly in the soil.

ISOLATION OF STREPTOMYCIN-PRODUCING ORGANISM

Streptomyces griseus (known until 1943 as *Actinomyces griseus*), the organism that produces streptomycin occurs in various soils and was first isolated in our laboratory in 1915 by myself and R. E. Curtis. This culture was not tested for its ability to produce any antibiotic, since such a possibility was not recognized at that time. More recently, however, the 1915 culture was shown to have possibly possessed the capacity of forming streptomycin, since, on irradiation, it yielded a streptomycin-producing mutant.

The isolation of streptomycin from the culture medium in which *Streptomyces griseus* was grown, its subsequent purification, and the study of its antibiotic spectrum were greatly facilitated by the previous isolation of streptothricin. The two years (1941-1943) of laborious study of the production, isolation and antibacterial activities of the latter contributed largely to the studies of streptomycin. It was found to be similar to its predecessor in physical properties, namely solubility in water, heat resistance, and favorable effect of an alkaline reaction. It was also similar chemically, namely its structure and nitrogen content, and biologically, including selective activity upon various bacteria and fungi, and in its resistance to bacterial decomposition.

ISOLATION OF STREPTOMYCIN AND ITS RECOGNITION AS CHEMOTHERAPEUTIC AGENT

The various steps and dates involved in the isolation of streptomycin are presented briefly in the following chronological order:

On August 20, 1943, one of my assistants, who was visiting the Department of Poultry Pathology at our Experiment Station in order to learn the techniques of virus research, was handed by the Pathologist a plate that had been swabbed with the contents of a chicken's throat. This was done in search of an organism that might be responsible for a disease in the chicken. When the incubated plated was examined, it was found to contain 3 colonies of an actinomycete.

When brought to me, I examinated the plate carefully and asked one of my graduate student to isolate the actinomycete colonies, and to test the cultures for their antibiotic-producing capacities. One of the cultures was found to possess considerable antibacterial potency. It was immediately identified as *Streptomyces griseus*, similar to the 1915 isolate, and was selected for further study. Another culture similar to the above was soon reported to have been isolated from a soil sample. In view of the abundant sporulation of this organism, the second isolation could easily have been a spore contaminant of the chicken throat culture.

A systematic study of the ability of the newly isolated *Streptomyces griseus* to produce an antibiotic substance was undertaken; several additional assistants and students were assigned to these experiments. When grown under various conditions and in different media, these cultures produced a new antibiotic; although similar in many respects to streptothricin, it was sufficiently different to be considered as a new antibiotic. It was named *streptomycin.*

Because of the methods developed previously in the study of streptothricin, we made rapid progress in the isolation, purification and concentration of the new antibiotic. In January, 1944, we made the first public announcement of the isolation of streptomycin. Simultaneously, we notified Merck & Co., a pharmaceutical company collaborating with us in the antibiotic program, calling their attention to the new antibiotic and its chemotherapeutic potentialities. We asked their help in producing immediately larger quantities of the material than we were able to do with our small scale fermenters and in purifying further the crude product.

Within three months after the announcement of the isolation of streptomycin Drs. William Feldman and H. Corvin Hinshaw of the Mayo Clinic visited our laboratory and suggested that streptomycin be made available to them for testing its effectiveness in experimental tuberculosis.

In August 4, 1944, we announced the activity of streptomycin in experimental animals, and in October, 1944, its important bactericidal properties.

The first results of effectiveness of streptomycin on the tuberculosis organism were published in November, 1944. This was soon followed (December, 1944) by the announcement by Drs. Feldman and Hinshaw of its potency in experimental tuberculosis. On October 5 and November 16, 1944, I delivered two public addresses, one at the Mayo Clinic and the other in New York, stressing the great potentialities of streptomycin as a chemotherapeutic agent.

The Food and Drug Administration in Washington immediately undertook the standardization of streptomycin. In July, 1945, I recommended a system of streptomycin units; this system was adopted by the Government agencies and by the streptomycin manufacturers as the standard.

The first comprehensive conference on streptomycin was arranged by Merck & Co., at their plant in Rahway, on June 20, 1945. This was later followed by the first extensive public conference on antibiotics, held at the New York Academy of Sciences on January 17, 1946. The report of the committee on chemotherapy of the National Research Council on the first 1 000 cases treated with streptomycin was published in September, 1956. Finally, on July 5, 1949, I published a comprehensive treatise on STREPTOMYCIN which I edited and in which more than 50 authors participated.

MANUFACTURE OF STREPTOMYCIN

Very little streptomycin was available for public use in 1945, since most of what was being manufactured was set aside for chemical, microbiological and animal investigations, and soon also for clinical evaluation. Large scale production was begun only in 1946, when licenses were extended to all manufacturers by the Rutgers Research and Edowment Foundation, to which the patent for the manufacture of this antibiotic was assigned. In March of that year, 26 kilograms of streptomycin where produced, the rate rapidly increasing, in November to 250. This production continued to increase in 1947, when 1 000 kilograms were manufactured in July and 1650 in December.

It may be of interest to note the allocations for June, 1947; in grams (Office of Materials Distribution, Department of Commerce):

Armed services	30 000
Other government agencies	42 000
Research	8 450
Civilian use (domestic)	546 450
Civilian use (foreign export)	100 00

The manufacture of streptomycin continued to rise in 1948, being 2 678 kilograms in July and 5 282 in December. These where actual sales figures and did not include total production, since a large part of the material, especially in the early months, went into experimental studies.

With and increase in the quantity of streptomycin becoming available, prices continued to drop, from about 25 dollars per gram in 1946 to $3.50 in March, 1947, and to less than 3 cents at this writing. Some official figures may be quoted here:

"On December 31, 1948, the nation's stockpile of streptomycin was 6 100 000 gm, the highest figure ever recorded. Production during 1948 rotated 37 000 000 gm, of which only 30 per cent was consumed by the domestic civilian market. Predicated on a reduction in price, wider application by the medical profession and availability of a less toxic product, the Department of Commerce anticipates demand and production of streptomycin in 1949."

During the first 6 months of 1949, manufacture of streptomycin ranged from 5 971 401 to 7 292 566 grams per month, or roughly at the rate of 80 000 kilograms a year, thus more than doubling the output for 1948. Although the American market was now receiving ample streptomycin, its production in the world at large was still on the upgrade. Numerous foreign plants have been built, including Canada, England, France, Sweden, Italy, Germany, India, Japan and the Soviet Union. Numerous other countries have been added later.

ANTIBACTERIAL PROPERTIES OF STREPTOMYCIN

From the very beginning of its isolation, streptomycin was found to be effective against various forms of tuberculosis, influenzal meningitis, tularemia of rabbit fever, genito-urinary infections, and numerous other infections caused by bacteria. It was soon recognized to have, however, certain limitations, notably a somewhat injurious effect upon the nervous system of some of the patients, and the potential development of resistance among sensitive bacteria upon prolonged contact with this antibiotic. Streptomycin was also found capably of supplementing penicillin in combating various bacterial infections.

CLINICAL EFFECTIVENESS OF STREPTOMYCIN

It would take far more space than is available here to discuss the clinical applications of streptomycin. Numerous books have been written on this subject in many languages. Most important proved to be its use in the treatment of tuberculosis. Streptomycin prompted one clinician to say: "We can now see the day when the 'white plague' of mankind may be eradicated" (See my book: "The Conquest of Tuberculosis," California Univ. Press. 1965.) Streptomycin proved to be effective in the treatment of many diseases caused by many bacteria which did not lend themselves previously to therapy. These also include infections which have become resistant to penicillin.

The discovery of streptomycin, following that of the sulfonamides and penicillin, has thus placed in the hands of the medical profession a highly important drug for combating numerous diseases that have plagued mankind since time immemorial. No wonder that the discovery of penicillin and streptomycin introduced to the popular mind the concept of "miracle drugs" and to the medical and veterinary professions the "Golden Age of Chemotherapy ".