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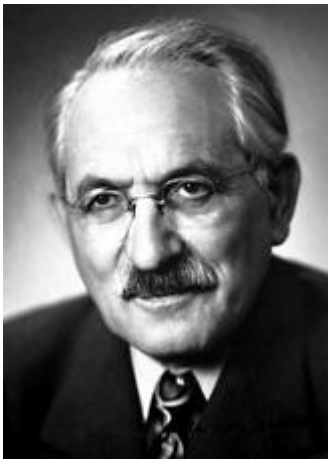
Nobel Prize in Medicines 1952



Selman Abraham Waksman

The Nobel Prize in Physiology or Medicine 1952 was awarded to Selman A. Waksman "for his discovery of streptomycin, the first antibiotic effective against tuberculosis".

Shortly after the discovery of the tubercle bacillus by Robert Koch in 1882 a search was made for an effective therapeutic agent against this germ. Eight years later Koch announced that he had succeeded in isolating a substance from tubercle-bacilli medium which he had found to be effective against tuberculous diseases. This substance is now known as tuberculin. Physicians throughout the world were most optimistic about this latest discovery by Koch, but this early optimism was soon dispelled when it was found that Koch's results could not be reproduced by other workers, and some of these workers found that tuberculin was dangerous when used in large doses.

A similar picture has occurred with all subsequent anti-tuberculous remedies. I will recall the short-lived triumph of sanocrysin and the sulpha compounds, promin, promizol, and diazone which were used in the States during the War and which were received at first with great enthusiasm. It is therefore quite natural for physicians to be sceptical when they heard that a new anti-tuberculous remedy called «streptomycin» had been produced in the United States in 1943. A

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decade has almost passed since this discovery and experiences from the whole world has proven that we have at last the first effective remedy against tuberculosis.

In contrast to the discovery of penicillin by Professor Fleming which was largely due to a matter of chance, the isolation of streptomycin has been the result of a long-term, systematic and assiduous research by a large group of workers. The initiator and leader of this group was Dr. Waksman. Dr. Waksman is the microbiologist at the Agricultural Department of Rutgers University in New Brunswick, New Jersey, and has been actively engaged on research work on soil microbes for many years, including their synergistic and antagonistic fight for existence. In 1939, i.e. one year before the rediscovery of penicillin by Florey and Chain, Dr. Waksman started an extensive programme of study which was aimed at determining the nature of the substance by which the various soil microbes destroyed each other. He had been interested in the actinomycetes for a quarter of a century, and it was only natural that he should first turn his attention to these microbes. In 1915 Dr. Waksman and one of his assistants had isolated from the soil a strain of actinomycete which they called Actinomyces griseus. This name was changed to Streptomyces griseus in 1943 and under this name it has now become world renowned. It is from a strain of this species that streptomycin is produced. Dr. Waksman had shown that of the microbes, Streptomyces was best able to survive when the living conditions in the soil became unsatisfactory, and this was an additional reason for commencing with theStreptomyces.

It has been known for a long time that the tubercle bacillus is rapidly destroyed in the soil. In 1932 Dr. Waksman was entrusted by the American National Association against Tuberculosis to make an investigation into this matter. He was able to confirm earlier observations and concluded that the disappearance of the tubercle bacilli in the soil was probably due to the influence of other antagonistic microbes. At that time the word antibiotic had not been coined. It was Dr. Waksman who introduced the new word «antibiotic», and it represents an antibacterial substance, produced by a microbe which is antagonstic in action to another.

In 1940 Dr.Waksman and his collaborator had succeeded in isolating the first antibiotic, which was called «actinomycin» and it was very toxic. In 1942 another antibiotic was detected and studied, called «streptothricin». This had a high degree of activity against many bacteria and also against the tubercle bacillus. Further studies revealed that streptothricin was too toxic. During the

streptothricin studies Dr. Waksman and his collaborators developed a series of test-methods, which turned out to be very useful in the isolation of streptomycin in 1943.

Encouraged by the discovery of streptothricin and stimulated by the triumphal development of penicillin treatment, the research team headed by Dr.Waksman continued their untiring search for new antibiotic-producing microbes. Before the discovery of streptomycin no less than 10,000 different soil microbes had been studied for their antibiotic activity. Dr. Waksman directed this work and distributed the various lines of research among his young assistants. One of these was Albert Schatz, who had previously worked with Dr. Waksman for 2 months and in June 1943 returned to the laboratory. Dr. Waksman gave him the task of isolating new species of Actinomyces. After a few months he isolated two strains of Actinomyces which were shown to be identical with Streptomyces griseus, discovered by Dr. Waksman in 1915. In contrast to the previous one the rediscovered microbe was shown to have antibiotic activity. To this antibiotic Dr. Waksman gave the name «streptomycin». He studied the antibiotic effect of streptomycin with Schatz and Bugie and found that it was active against several bacteria including the tubercle bacillus. These preliminary studies were completed in a relatively short time, thanks to the clear principles which had been set out previously by Dr. Waksman for the study of streptothricin.

The subsequent testing of streptomycin as an anti-tuberculosis remedy was entrusted to two physicians, Feldman and Hinshaw, at the Mayo Clinic in Rochester. From experiences with sulpha compounds they had developed a reliable research technique. As a result of very promising work with experimental tuberculosis in guinea pigs, Feldman and Hinshaw considered it appropriate to try its activity in human tuberculosis. They selected a series of cases in which spontaneous recovery was regarded as hopeless. The most surprising result was the apparent curative action of streptomycin in two extremely severe cases of tuberculous diseases, viz. tuberculous meningitis and miliary tuberculosis. Encouraged by this experience they ventured to treat more benign and recent cases of tuberculosis and these were improved considerably.

In the meantime Dr. Waksman and his associates continued with their researches. They found that different strains of Streptomyces griseus varied in their capacity to produce antibiotic substances. Out of all isolated strains of this microbe, only four were adapted for the production of streptomycin on a large scale. Streptomyces griseus grows on many different media, but streptomycin can only be produced under certain conditions. Dr. Waksman and his co-workers

made preliminary chemical studies in order to determine the formula of streptomycin. The great work of Folkers and Wintersteiner in this field of research gave us the chemical formula, which led to the isolation of streptomycin in pure form.

The activity of streptomycin is principally bacteriostatic, i.e. it checks the bacterial growth and is in some degree also bacteriolytic, i.e. it destroys the tubercle bacillus. The mechanism of this important antibacterial effect is not yet known.

At the present time streptomycin has had such a widespread and a long trial throughout the world that it is now possible to form a fair opinion of its therapeutic value. The most sensational effect is seen in the treatment of miliary tuberculosis and tuberculous meningitis. The former had previously had a fatal outcome with few exceptions and meningitis has always been fatal. Nowadays the prognosis is far better, thanks to streptomycin. The immediate result with streptomycin treatment of tuberculous meningitis can be dramatic; patients that are unconscious and have a high fever may improve rapidly after administering the drug. The ultimate result in such severe cases is not so satisfactory. The earlier the streptomycin treatment is started the greater the chance of recovery. The outcome of streptomycin treatment is therefore dependent on an early diagnosis of the tuberculous disease. This circumstance can explain the great difference in the reported results by different workers, ranging from 75% recoveries in the most favourable cases to 20% in the more severe. Miliary tuberculosis is more amenable to streptomycin treatment than meningitis. According to recent experiences one can reckon with a definite healing in about 80%.

Early cases of pulmonary tuberculosis may be successfully treated with streptomycin. In cases of pulmonary tuberculosis suitable for surgery, streptomycin has proved a very valuable supplement. By means of streptomycin it has been possible to transform patients into a suitable condition for operation, which before streptomycin treatment would have been considered impossible. In the treatment of tuberculosis of the genito-urinary tract and in bone and joint tuberculosis, streptomycin has been of considerable value. Thanks to the possibility of pre- and postoperative chemotherapy, new and more conservative principles for the surgical treatment have been applied with success.

Streptomycin is not altogether a harmless remedy, but with greater experience with this antibiotic, methods have been devised to minimize this effect. The untoward effects that have been reported previously, viz. damage to the vestibular and auditory nerves, have been greatly reduced

or abolished by using purified streptomycin, smaller doses and shorter periods of treatment. These side-effects cannot be regarded nowadays as a contraindication to streptomycin treatment.

Another complication is the development of strains of bacteria that become more and more resistant to streptomycin. This very important question has been studied in many centres, and different ways have been tried to prevent the development of streptomycin-resistant bacteria. It has been shown that in combination with other anti-tuberculous compounds, especially PAS, the chemotherapeutic remedy detected by the Swedish biochemist Lehmann, the development of streptomycin resistance is delayed.

I have dealt almost exclusively on streptomycin as an anti-tuberculous remedy, because it is this activity which has justified being awarded the Nobel Prize. However, streptomycin has a much more extensive antibacterial action and has been successfully used against a large number of the common pathogenic bacteria, including several not affected by penicillin. The value of streptomycin as a remedy against infectious diseases in humans is therefore much greater than may appear from this presentation of its antituberculous effect.

By the discovery of streptomycin Dr. Waksman and his collaborators have made a very important contribution to the history of medicine. Even if streptomycin is not the perfect anti-tuberculous remedy, its introduction nevertheless signifies a gigantic step forward. Above all, its isolation has suggested procedures for future investigations that may guarantee fundamental results. One may hope that this approach will lead in the near future to the eagerly expected goal, viz. a remedy that will make possible the eradication of tuberculous disease.

Professor Selman Waksman. The Caroline Medical Institute has awarded you this year's Nobel Prize for Physiology or Medicine, for your ingenious, systematic and successful studies of the soil microbes that have led to the discovery of streptomycin, the first antibiotic remedy against tuberculosis. Neither are you a physiologist nor a physician, but still your contribution to the advancement of medicine has been of paramount importance. Streptomycin has already saved thousands of human lives. As physicians, we regard you as one of the greatest benefactors to mankind. It is my privilege to extend to you on behalf of the Caroline Institute our most sincere felicitations to your scientific achievements and to congratulate you on your award. Professor Waksman, I now request you to receive your Nobel Prize, from his Majesty the King.

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