

History of Medicine

Correspondence with a pioneer, Jürgen Lehmann (1898 - 1989), producer of the first effective antituberculosis specific

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Summary

Correspondence between the author and Lehmann provided evidence that the latter evolved the first effective antituberculosis drug, para-aminosalicylic acid (PAS), contrary to accepted belief that this honour belonged to Nobel Prize-winner Selman A. Waksman for his production of streptomycin. While both drugs appeared in 1943, successful animal and clinical trials of PAS preceded those of streptomycin. PAS has been discarded in modern treatment regimens because of gastric side-effects, but was available at a critical time to demonstrate the principle of multiple therapy in prevention of bacterial resistance in tuberculosis therapy. It probably saved streptomycin, which causes bacterial resistance and clinical regression within 3 months when used alone, from being discarded as an unsuitable drug of temporary benefit and a public health hazard.

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Medical opinion accepts the antibiotic streptomycin, produced in the USA in 1943 by Selman Waksman (1888-1973), as the first effective antituberculosis drug. This earned him the Nobel Prize in 1952. Evidence exists that priority of proved clinical effectivity against tuberculosis should be accorded the chemotherapeutic agent para-aminosalicylic acid (PAS) evolved by Jürgen Lehmann of Sweden (Fig. 1). This claim stands, despite the two drugs appearing in 1943 and their laboratory and clinical trials occurring nearly concurrently.

Initial disclosures

Lehmann's¹ first publication of his clinical trials on PAS were published in *The Lancet* in 1946 as a preliminary communication. He reported improvement with the local application of PAS solutions in tuberculous fistulas, abscesses and empyemas. The second part of his report was on PAS oral therapy of 20 lung tuberculosis patients from March to October 1944. His findings were cautious but optimistic — fever decrease, appetite improvement, weight gain and a raised erythrocyte count. (Lehmann's disclosures occurred about 2 years after the trials.) He provided confirmatory evidence of the early promise of the efficiency of PAS in an editorial² published in 1964 as a historical review in *American Review of Respiratory Disease*. This included a presentation at a meeting of the Scandinavian Physiological Society in 1946 of 82 patients treated with PAS by Vallentin and himself, as well as a survey of Lehmann's publications in *Diseases of the Chest* in 1949 and

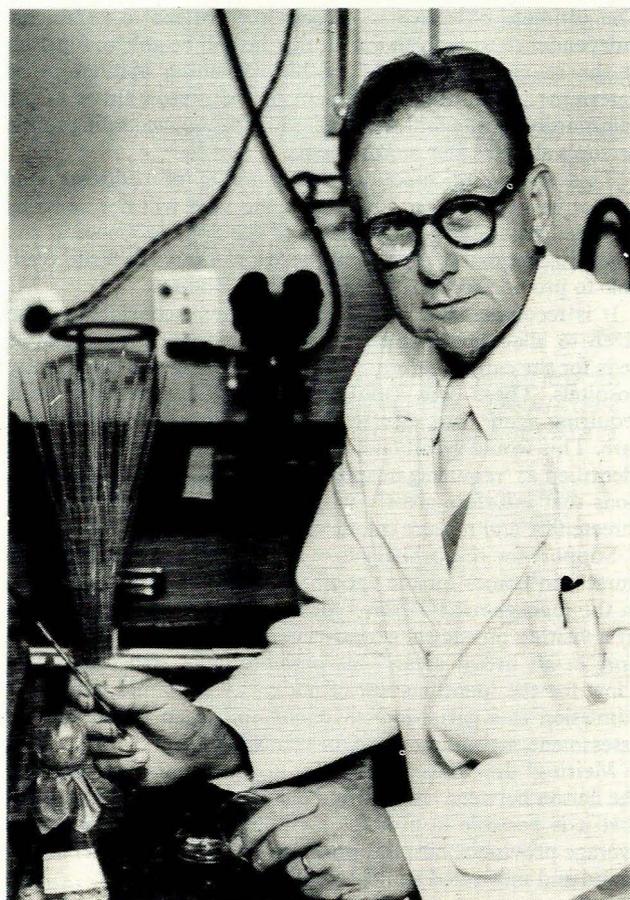


Fig. 1. Jürgen Lehmann, 1898-1989.

in *Tubercle* in 1950 of the results of 378 patients treated with PAS in six Swedish sanatoriums. He also referred to his address at the Seventh Streptomycin Conference in Denver in 1949 in which he provided a state of the art of the Swedish PAS experience including problems of PAS administration and the determination of blood levels and bacterial resistance. This was followed by a matched-case comparison of effectivity of 205 Swedish patients treated with PAS and 223 patients treated with streptomycin by the Veterans' Administration of the USA in 1947. PAS caused a slower regression of pulmonary infiltrations radiologically than streptomycin, but had a better effect on lowering temperature and erythrocyte sedimentation rate. Streptomycin had the advantage in weight gain and sputum conversion but presented a serious problem of 8th nerve toxicity of permanent deafness and vestibular damage. PAS, despite large average oral doses of 14 g/d caused no toxic problems, only gastric irritation that improved by using enteric coated granules instead of the tablets. Lehmann pointed

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out that the major disadvantage of streptomycin was that 80% of patients developed bacterial resistance within 3 - 4 months, with clinical regression. With PAS this problem was negligible and of slight degree occurring only after 3 - 6 months of treatment.

Lehmann concluded his historical review by claiming, with supporting dates, that the first animal trials with PAS were done 3 months before those of streptomycin and the first clinical trials of 20 patients nearly 8 months before, and said: 'In reality PAS was used before streptomycin and this is the first active chemical agent in the treatment of tuberculosis.'

The motivations for the discoveries of PAS and streptomycin differed basically. The evolution of PAS was based on the finding by Bernheim³ in 1940 that salicylic acid stimulated the oxygen uptake of the tubercle bacillus. Considering that closely related compounds could have an inhibitory effect on the metabolism of the bacillus, on the principle of competitive antagonism, Bernheim tried 49 variations of salicylic acid and related compounds between 1941 and 1943 without success. Continuing this line of research, Lehmann achieved success after more than 50 variations when he asked the Ferrosan pharmaceutical firm in March 1943 to place an amino group in the para position of the benzene ring of the salicylic acid molecule, creating para-aminosalicylic acid (PAS).

Although this synthesis proved difficult, with only 13 g becoming available by December 1943, PAS was shown to inhibit growth of *Mycobacterium tuberculosis* on culture. After animal studies on infected rabbits and guinea-pigs showed therapeutic response and lack of toxicity, the clinical trials began in March 1944.

Contrasted with Lehmann's logical and continued line of research, the role of Waksman in the production of streptomycin could be considered sporadic and somewhat detached. He was not a physician and, as professor of soil microbiology at the small agricultural college of Rutgers, his primary concern and life-long interest was the study and teaching of the role of soil micro-organisms in the breakdown of plant and animal residues in the maintenance of soil fertility. He used post-graduate students to do the research, in interrupted periods, which led to the discovery of streptomycin. This started in 1932 when the National Tuberculosis Association asked him to investigate the fate of tuberculosis germs in the soil. Comroe⁴ states that streptomycin would have been discovered much sooner had not Waksman missed several clues over the years; particularly in 1935 when the poultry pathologist at Rutgers asked him to identify an organism isolated from the throat of a sick chicken, which had killed and replaced tubercle bacilli on culture by contamination. This was *streptomyces griseus* from which, in 1943, Waksman isolated streptomycin. Waksman later admitted that he did not take advantage of this observation being preoccupied with soil fertility studies. Even in January 1944 when his group published⁵ the cultural activity of the recently discovered streptomycin against 22 pathogens, including inhibition of growth of *M. tuberculosis*, the profound significance of a potential antibiotic effective against the tubercle bacillus was not noted by the authors. Similarly, the group's next paper⁶ in August 1944 tested the activity of streptomycin on mice infected with various Gram-negative bacteria but not with *M. tuberculosis*. Streptomycin may have been lost to tuberculosis treatment for many years had not Feldman and Hinshaw of the Mayo Foundation, aware of Waksman's antibiotic research and his limited facilities, and seeking potential tuberculosis agents for animal research, offered to do animal studies for him. From April 1944, when Waksman supplied them with 10 g of streptomycin, subsequently supplemented by the Merck Co. who took over the manufacture and patent rights, to September 1944, Feldman and Hinshaw proved the effectiveness of streptomycin on tuberculosis-infected guinea-pigs. The first patient to receive

streptomycin was a 21-year-old woman with advanced tuberculosis. She was treated with interrupted courses of streptomycin by Dr K. Pfuetze at the Mineral Falls Sanatorium from November 1944 to April 1945. She improved remarkably with arrest of the disease 2 years later. This good result contrasted with the negative report by Hinshaw *et al.*⁷ of an uncontrolled study of 100 cases in 1946. They found streptomycin 'encouraging' but not recommended for patients 'making satisfactory progress or likely to achieve arrest of their disease as a result of conventional therapeutic methods'.

The correspondence

As an apparent injustice to Lehmann existed of lack of recognition as the developer of the first effective drug for tuberculosis, the author wrote to the laboratory where Lehmann had done his research for early data on PAS. A reply was received from Lehmann who provided personal information and comprehensive reprints. This started a correspondence with Lehmann who was then 88 years old and did his own typing. The following extract is taken from the first letter with spelling corrected.

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March 10, 1986

Dear Dr Dubovsky,

Your letter to the Director of the Central Laboratory at Sahlgrens Hospital was forwarded to me. It was the most remarkable letter I have received for many years. You are the first outside Sweden who has paid attention to the fact that PAS was in clinical use before streptomycin, eight months before. . . . Perhaps you wonder why I published the first paper on PAS so long after it was taken in clinical use. The reason was that as Ferrosan, a small company had not taken out a patent on PAS, I didn't dare to publish the formula on PAS as other greater companies could take over the production of PAS. . . .

When Waksman, whom I met at international congress, had got the Nobel Prize, I cabled congratulations to him. Two weeks later I got a letter from him in which he mentioned that he expected that we get the prize together. In the international literature very little attention is paid to PAS and this has been very disappointing to me as I have published papers in which I have pointed out that PAS was the first remedy effective against tuberculosis. . . . I have to thank you for your kind letter which I found highly encouraging to me.

Sincerely yours,
Jürgen Lehmann

Three more letters followed with more information enabling the author⁸ to publish and send to Lehmann a comparative study of the history of PAS and streptomycin. A reply was received from his wife on 12 August 1988 conveying thanks from her husband who was unable to reply on account of general debility. Another letter from her advised that Lehmann passed away on 26 December 1989 in an institution for frail care a few weeks short of his 92nd birthday.

Jürgen Lehmann

Lehmann's family had an academic background. His father and grandfather, respectively, held chairs in the history of theology and in ophthalmology. His hobbies were art, painting and music. He was born in Copenhagen and qualified in medicine at the University of Lund. He started his academic

career in 1920 and worked at various universities in Scandinavia, holding chairs in physiology, biochemistry and pharmacology. Enzymes and analytical methods were the main fields of his research, and he carried out original studies in the use of vitamin K in haemorrhage of the newborn, the estimation of vitamin B₁ levels in the diagnosis of beri-beri, the use of dicoumerol in thrombosis and the role of tryptophane deficiency as a cause of psychosis. At the time of his discovery of PAS, Lehmann was head of the laboratory of the Sahlgrenska Hospital in Göteborg, Sweden.

The significance of PAS

The major contribution of PAS to tuberculosis therapy was that it was available at a critical period to establish the principle of multiple therapy in preventing bacterial resistance. The British Medical Research Council,⁹ testing three concurrent groups on PAS alone, streptomycin alone and PAS and streptomycin, felt obliged in 1949 to publish a preliminary report of great importance; the combination of PAS and streptomycin considerably reduced the risk of the development of bacterial resistance to streptomycin. The Council¹⁰ further found, in 1955, that in including the recently discovered INH in trials that while the combination streptomycin + INH was more effective therapeutically than PAS + INH, the latter combination was preferred, since it was more effective in preventing bacterial resistance. It could be said that PAS formed an important bridge of bacterial resistance prevention between the discoveries of streptomycin in 1943 and INH in 1953. Without this link, streptomycin might have been discarded as a drug of temporary benefit followed by clinical decline and the emergence of the epidemiological hazard of bacterial resistance of the tubercle bacillus. The combination streptomycin + PAS + INH as 'triple therapy' became standard effective treatment until about 1970, when PAS was replaced, because it caused gastric irritation, by more convenient drugs.

Conclusion

Lehmann was hurt by lack of recognition as the discoverer of the first effective antituberculosis specific. This could be

basically ascribed to lack of publicity due to his delay of 2 years in publishing his clinical trials. A contributory factor was the small quantities of PAS made available in the early years of its use due to the limited facilities of the Swedish manufacturing firm. In contrast, streptomycin was more freely available at a corresponding period as manufacture was taken over by the large Merck company. The ease of use of streptomycin as an intramuscular injection in contrast with the gastric problems of PAS favoured its acceptance. Birath¹¹ provides an additional reason for the delayed acceptance of PAS — the scepticism of Swedish doctors in 1946 when the results were first made known; they suspected that the beneficial effects were due to salicylic acid's known antipyretic action rather than a specific antituberculosis one.

REFERENCES

1. Lehmann J. Preliminary communication: para-aminosalicylic acid in the treatment of tuberculosis. *Lancet* 1946; 1: 15-16.
2. Lehmann J. Twenty years afterward: historical notes on the discovery of the antituberculosis effect of para-aminosalicylic acid (PAS) and the first clinical trials. *Am Rev Respir Dis* 1964; 90: 953-956.
3. Bernheim F. The effect of salicylate on the uptake of the tubercle bacillus. *Science* 1940; 92: 204.
4. Comroe JH. The story of streptomycin (Part II). *Am Rev Respir Dis* 1978; 117: 957-967.
5. Schatz A, Bugie E, Waksman SA. Streptomycin, a substance exhibiting antibiotic activity against Gram-positive and Gram-negative bacteria. *Proc Soc Exp Biol Med* 1944; 55: 66-69.
6. Jones D, Metzger HJ, Schatz A, Waksman SA. Control of Gram-negative bacteria in experimental animals by streptomycin. *Science* 1944; 100: 103-105.
7. Hinshaw HC, Feldman WH, Pfuetze KH. Treatment of tuberculosis with streptomycin: a summary of observations on one hundred cases. *JAMA* 1946; 132: 778-782.
8. Dubovsky H. The history of para-aminosalicylic acid, the first tuberculosis antimicrobial agent, and streptomycin: a comparative study. *Adler Museum Bull* 1988; 14: 7-11.
9. Medical Research Council Investigation. Treatment of pulmonary tuberculosis with para-aminosalicylic acid and streptomycin. *Br Med J* 1949; 2: 1073.
10. Medical Research Council Investigation. Various combinations of isoniazid with streptomycin or with PAS in the treatment of pulmonary tuberculosis. *Br Med J* 1955; 1: 435.
11. Birath G. Introduction of para-aminosalicylic acid and streptomycin in the treatment of tuberculosis. *Scand J Respir Dis* 1969; 50: 204-209.