TECHNICAL PAPERS

The Remote Sustained Threshold Therapeutic Action of Streptomycin in Tuberculosis

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The use of streptomycin as a therapeutic agent in tuberculosis has posed many problems. It is believed such problems cannot be solved by human therapeutic use but, of necessity, must be founded basically in the intimate mechanisms of its actions in tuberculosis. Therefore, exacting and carefully planned animal experimentation will be required for elucidation. Although suspected of acting in the animal economy as it does in the test tube, there are many discrepancies between so simple an explanation and observed facts.

In previous communications (*1*, *2*) it was shown that streptomycin is not capable of destroying either virulent or avirulent human tubercle bacilli in the body and that maximum tolerated doses in guinea pigs (or other laboratory animals) cannot completely retard the development of the tubercle bacilli or tuberculosis following intravenous infection. However, it does exert a definite and fairly consistent partial retarding effect on the development of tuberculosis in animals in appropriate doses, and therefore must be considered an adjuvant treatment for this disease at present under certain limitations prescribed by necessary sanatorium and hospital regimes or supervision.

Streptomycin cannot be considered an inert or nontoxic therapeutic agent in itself, and therein lies the question of the appropriate, the maximum, and the most efficient dose to attain the maximum therapeutic benefit, acknowledging that it is an adjuvant agent against tuberculosis in man. On the toxicological and pathological side there is every reason to believe that those early enthusiasts who saw little detrimental effect from its use for short periods of time considered only spectacular effects in man as significant. It was noted that "early side reactions have not been alarming, and no late toxic effects have so far been observed" (*7*); or, "In this limited experience, tests of renal and hepatic function together with blood studies before and after the parenteral administration of streptomycin revealed no evidence of serious toxicity. Reactions, consisting of fever, arthralgias, and skin rashes as well as histamin-like effects, are believed to be due to impurities retained in the preparations of streptomycin employed in these studies" (*4*). A better interpretation of the toxicity, in 1946, seemed to be that "streptomycin as well as its impurities are pharmacodynamically very active compounds. A more detailed knowledge of their toxicologic properties is a matter of great importance" (*5*). Reporting more recently from studies with streptomycin administration in tuberculosis in man, the conclusion is drawn that "as streptomycin can produce potentially serious toxic reactions it is inadvisable to use the drug in the treatment of generally benign infections, such as recently acquired pulmonary tuberculosis of minimal extent" (*3*). A more strictly pathological study on normal animals (monkeys, dogs, rats, mice, chickens, and guinea pigs) indicated a toxicity of low order, but large doses produced focal necroses in the lungs in dogs, fatty metamorphosis in the kidneys of monkeys and dogs, and neurotoxic effects in dogs (*6*).

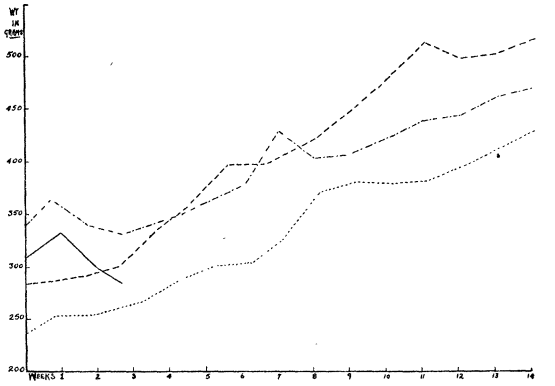

FIG. 1. Average weight chart of streptomycin-treated animals: ——— infection controls; ---------- 4 daily doses; — — — 1 daily injection; — - — - — 5-day interval injection.

The following report on the effect of streptomycin in tuberculosis is not intended to be final or complete and is presented with the full recognition of a definite effect of streptomycin as a partial retardant to tuberculosis. For this presentation it is limited to the guinea pig, the animal in which this retardant effect of streptomycin was first demonstrated. The information disclosed may be valuable for the proper therapeutic use of streptomycin in man as well as extending the appropriate use of this drug, which is still limited in production and economically beyond the reach of some institutions and tuberculous individuals. It must be recognized at the outset that these results are those of a set, controlled experiment in which the bacilli were introduced into young, normal animals. Such effects of streptomycin on tuberculosis as are noted here might occur in the naturally infected and relatively immune tuberculous man far less definitely and consistently, although the significance of the dosage of streptomycin would in all probability be the same and could be applied to man without exaggeration. If we now use the two most conspicuous effects of streptomycin in tuberculosis (the prolongation of life and the retardation of the disease in the guinea pig) as a criterion, it will be possible to approximate the relative value and efficiency of different modes of treatment, comparatively speaking, with streptomycin in tuberculosis. Without elaborating upon details, the following findings with streptomycin treatment were noted, using for this study only the best, purest, and highest unit titer streptomycin obtainable at present. All the streptomycin used rated at about 1,000,000 units/gram.

In all the infections in these experiments, a highly virulent strain of human tubercle bacilli (#4008) was used, and a standard amount (1 mg.) of fine suspension was injected intravenously into the ear vein. All treatments with streptomycin were given by subcutaneous injection.

In a series of preliminary experiments in which the persistence of streptomycin effect was studied, using a sufficiently large number of controls (6) and an equal number of streptomycin-treated animals (given 25,000 units of streptomycin daily for 82–91 days and infecting intravenously one day after the last treatment), the average duration of life of the controls was 22 days compared with 29 days for the pretreated animals. When the pretreatment with a similar amount of streptomycin daily continued for only two weeks, the average duration of life of the controls was 21 days; and for animals pretreated with streptomycin, it was 22 days, which is about the same, although the spleen size was preceptibly less in the treated animals. In single injections, 50,000 units of streptomycin were not lethal, while 100,000 units were frequently fatal in our tests on normal animals.

In order to compare the results of the injection of 4 doses of streptomycin daily for a total of 25,000 units with a single injection of 25,000 units daily and 25,000 units given at 5-day intervals in a single injection, several sets of duplicate experiments were performed. Four to 6 or more guinea pigs were used in each test as well as infection control animals given only the intravenous injection of 1 mg. of virulent human tubercle bacilli in fine suspension without treatment with streptomycin. While the average duration of life of the control infected guinea pigs varied within the narrow limits of 19–21 days, that of the animals given 4 daily injections to a total of 25,000 units daily was from about 100 to about 150 days. Those given the 25,000 units at 5-day intervals, starting 6 days prior to infection and continuing throughout infection, were also alive beyond 100 days in most instances.

In these experiments it was noted that individual animals would die of a generalized tuberculosis in spite of intensive treatment with streptomycin and regardless of whether the injections were given daily or at 5-day intervals.

The appended 14-week weight graph (Fig. 1) illustrates the effects of 4 daily injections (for a total of 25,000 units) of streptomycin, one single daily injection throughout the experiment, and single injections of streptomycin at 5-day intervals compared with infection controls. In the series in which the streptomycin was given only as a single injection of 25,000 units at 10-day intervals, the treated animals outlived the controls, so that the average of the controls was 20 days and that of the treated 70 days.

The foregoing experiments would appear to indicate that streptomycin does not act in tuberculosis as a simple chemotherapeutic retardant as it does in the test tube (since simple *in vitro* acting and *in vivo* distributed chemicals fail to affect tuberculosis), but that there is a threshold of remote sustained action. When initiated minimally, the effect persists for some time; above the maximum threshold effect, it is needless to continue forcing treatment, since the benefit derived does not exceed that of the established maximum. This information should extend the present use of streptomycin as an adjunct to the treatment of human tuberculosis and make streptomycin available for human treatment where excessive administration previously was economically prohibitive to certain cases.

It would appear that the amount and frequency of administration of streptomycin in tuberculosis can be reduced without appreciable loss of effectiveness. It is felt that the intimate mechanism of streptomycin action in tuberculosis still remains to be disclosed satisfactorily.

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A Possible Role of Food Purification in the Etiology of Dental Caries

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A study (*3*) has been made of factors influencing the caries susceptibility of rodents (36 mice, 53 Syrian hamsters, and 153 Long Evans strain rats). It has been possible to produce dental caries similar to that in man by feeding a finely powdered, purified ration (*1*) containing 67 per cent purified carbohydrates, primarily sucrose, and complete in known nutritional essentials. Caries did not develop in the mice and rats and was limited in the hamsters unless the experimental feeding on the purified diet was commenced during tooth development.

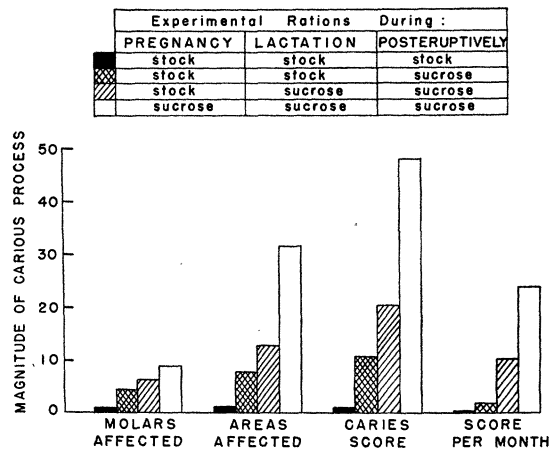

Fig. 1. The caries incidence of groups of hamsters whose experimental feeding on the purified ration was commenced *before*, *during*, and *after* tooth developments, respectively; their molars decayed in a ratio of 20:10:2. ("Sucrose" diet refers to the purified ration, containing 67 per cent sucrose. "Stock" diet refers to the Purina laboratory chow.)

The caries susceptibility appears to be greatly influenced by a mechanism (possibly an unrecognized nutritional factor) operating before tooth eruption from conception to maturation of the offspring and their individual teeth (see Fig. 1). In the light of these results a reinterpretation has been made of earlier observations in animals and man.

A review of previous failures to produce caries in various animals (*3*), including the primate, fed purified high sucrose diets suggests that the experimental feeding started out with