Comments on Bacterial Resistance to Streptomycin*

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Shortly after streptomycin was introduced in the treatment of tuberculosis, two major obstacles to its value as a therapeutic agent became apparent. These were, vestibular damage and development of bacterial resistance. With the reduction in the daily dosage from 2 gm. and higher, to 1 gm. and later to 0.5 gm., serious vestibular damage has been eliminated. However, development of bacterial resistance, which is apparently due to duration of treatment rather than to dosage, remains for the present the most serious threat to successful streptomycin therapy in tuberculosis. With the appearance of resistant forms of tubercle bacilli, streptomycin ceases to be an effective therapeutic agent not only for the individual patient but also for those to whom he may transmit the disease.

Youmans and Williston† found that when a group of mice were injected intravenously with 0.1 mg. of a culture of tubercle bacilli isolated from a patient with pulmonary tuberculosis, streptomycin had a marked suppressive effect on the infection produced in the animals. On the other hand when a group of mice were injected in the same manner with a culture of tubercle bacilli from the same patient after he was treated with streptomycin, the infection resulting from it was uninfluenced by the drug.

Bogen‡ related the case of a nurse who contracted tuberculosis while working with streptomycin treated patients. Tubercle bacilli recovered from this case were resistant to 1000 micrograms per cc. on original isolation.

It is obvious why the study of bacterial resistance to streptomycin and specifically the search for measures to prevent it are occupying a very prominent place in this field of investigation.

The theory behind the development of bacterial resistance to streptomycin is based on the knowledge that probably every case of tuberculosis harbors different varieties of tubercle bacilli. By

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far the vast majority of organisms are sensitive to streptomycin but an occasional form is by nature resistant to the drug. It is undoubtedly for this reason that a favorable initial response to streptomycin is shown by almost every patient who has active and progressive tuberculosis and is not moribund and that, if treated long enough, probably every case acquires resistance to streptomycin sooner or later.

It may be reasoned that under streptomycin therapy all the sensitive organisms are inhibited and are either prevented from multiplying altogether or their rate of reproduction is greatly reduced. Thus the army of invaders becomes reduced at a fairly rapid rate when exposed to the drug. While the vast number of sensitive organisms are thus held in check by streptomycin, the natural defensive forces of the body come into play, assume dominance, and begin to recover lost ground. It is apparent then that the time during which effective use of streptomycin can be made is limited to the minimum time required by the streptomycin resistant organisms to increase in sufficient numbers to become a potent force against which streptomycin is a useless weapon.

No relationship has been found to exist between the degree of sensitivity of tubercle bacilli to streptomycin and the degree of their virulence. Either variety may be of high or low virulence. Both varieties work hand in hand and each contributes its share to the clinical picture in proportion to its numerical strength as well as to degree of virulence.

The rationale of the various methods proposed for combating the development of resistance is predicated upon the speed with which the enemy must be overcome. In other words this must be a "blitz" campaign which would enable the patient to overcome the disease in the shortest possible time before the streptomycin resistant organisms can multiply sufficiently to become effective and to take over the situation.

Since resistant strains of tubercle bacilli usually begin to make their appearance before the end of the second month of treatment, shorter periods of treatment than 60 days have been advocated and are being tried. Simultaneously other drugs such as promizole and para-aminosalicylic acid are being investigated for the value they may have as auxiliary weapons against the tubercle bacilli, with the hope that they may act on the resistant forms when administered in conjunction with streptomycin.

It is also hoped that further research may bring forth other antibiotics which could be used for the treatment of tuberculous patients whose organisms have become resistant to streptomycin.

Meanwhile a plea is made against the indiscriminate use of streptomycin as a so-called "additional boost" for the treatment
of comparatively mild tuberculous lesions which are very likely to regress or have already shown evidences of satisfactory regression both clinically and roentgenologically under adequate conventional therapy. Abuse of the drug may deprive the patient of its benefits should he ever need it more urgently. It also helps to perpetuate in the community a form of tuberculosis on which streptomycin has no effect. While administering to the individual patient, the public health interests must not be lost sight of.

REFERENCES
2 Bogen, Emil: Report During Round Table Discussion on "Dosage of Streptomycin" at Fourteenth Annual Meeting, American College of Chest Physicians, Chicago, June 20, 1948.