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Effect of Streptomycin on Experimental Infections Produced in Mice with Streptomycin Resistant Strains of *M. tuberculosis var. Hominis.**

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Youmans, Williston, Feldman and Hinshaw[1] have shown that virulent tubercle bacilli may acquire resistance to the *in vitro* bacteriostatic action of streptomycin, either by prolonged exposure to streptomycin in the test tube, or in patients undergoing treatment with this agent. These findings raise the important questions of whether these streptomycin resistant tubercle bacilli are still pathogenic and, if so, whether they are equally resistant to the bacteriostatic action of streptomycin while producing infection in a susceptible animal.

Methods. Eighty white mice† weighing approximately 25 g each were divided into 4 groups of 20 mice each. The first group was injected intravenously with 0.1 mg of a suspension of a 21-day-old culture of a streptomycin sensitive H37Rv strain. The second group was injected similarly with 0.1 mg of a 21-day-old culture of an H37Rv strain which had become resistant to more than 1000.0 μg of streptomycin per ml following exposure to streptomycin *in vitro* (designated H37RvR). The third group was injected intravenously with 0.1 mg of a cul-

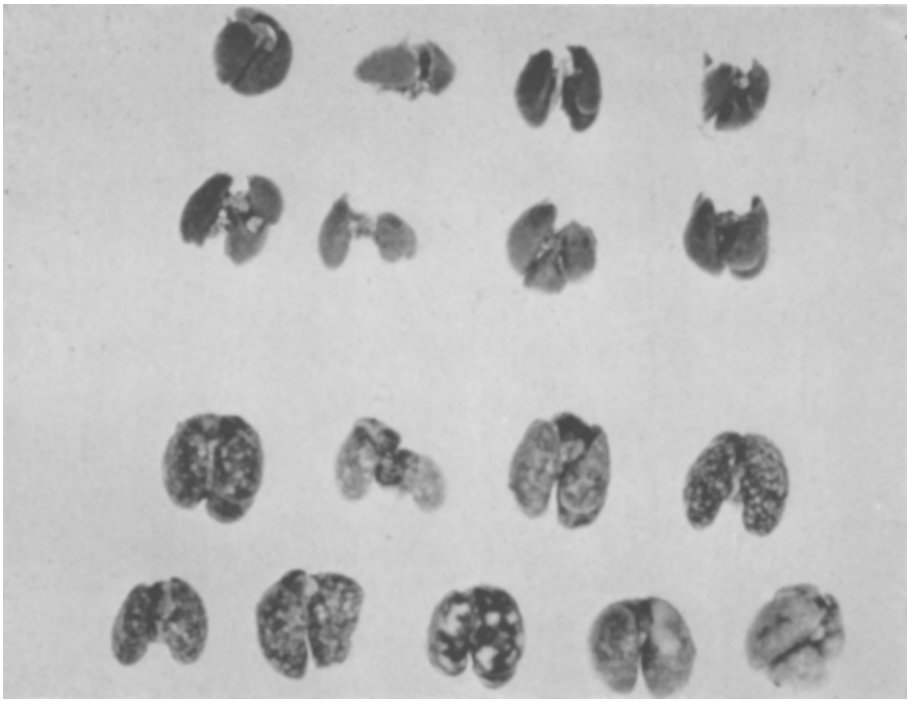

FIG. 1.
Lungs of mice infected with streptomycin sensitive strain H37Rv. Upper 2 rows, streptomycin treated. Lower 2 rows, no treatment.

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The streptomycin was furnished through the courtesy of Dr. L. A. Sweet, Parke, Davis and Company, Detroit, Mich.

1 Youmans, G. P., Williston, E. H., Feldman, W. H., and Hinshaw, H. C., *Proc. Staff Meet. Mayo Clinic*, 1946, **21**, 126.

† Strong A strain.

TABLE I.
Effect of Streptomycin in Mice on Streptomycin Sensitive and Streptomycin Resistant Strains of *M. tuberculosis var. hominis.*

Organism	Streptomycin sensitivity *in vitro* (μg/ml)	Amt streptomycin inj. daily (μg)	No. of mice	No. dead	% mortality	Avg amt of gross pulmonary tuberculosis
1. H37Rv	0.78	3000	8*	0	0.0	None
2. H37Rv	0.78	None	10	6	60.0	+++
3. H37RvR	1000.0	3000	10	10	100.0	++++
4. H37RvR	1000.0	None	10	10	100.0	++++
5. 15	0.78	3000	9†	0	0.0	None
6. 15	0.78	None	9†	6	66.0	+++
7. 67	1000.0	3000	10	5	50.0	+++
8. 67	1000.0	None	9†	5	44.0	+++

* Two mice died day after injection.
† One mouse died day after injection.

ture isolated from a patient with pulmonary tuberculosis (strain 15). The growth of this culture was inhibited *in vitro* by less than 1.0 μg of streptomycin per ml. The fourth group was injected intravenously with 0.1 mg of a culture isolated from the same patient after several months treatment with streptomycin (strain 67). At this time this culture grew readily *in vitro* in a concentration of streptomycin of 1000.0 μg per ml.

Half of the mice in each group served as controls whereas the other 10 mice were

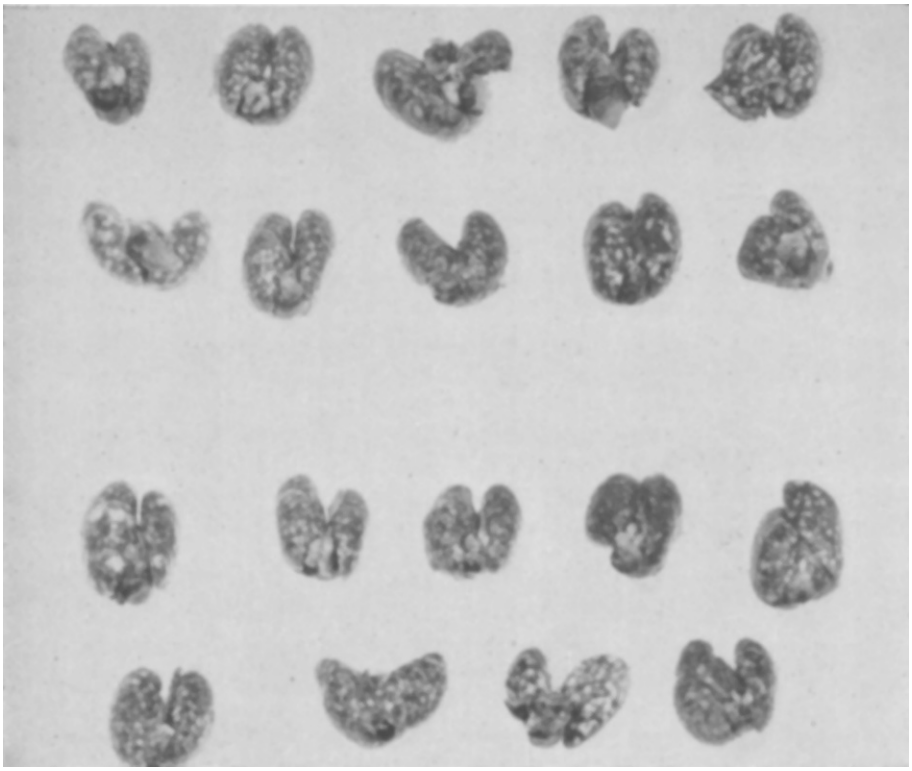

FIG. 2.
Lungs of mice infected with streptomycin resistant H37RvR. Upper 2 rows, streptomycin treated. Lower 2 rows, no treatment.

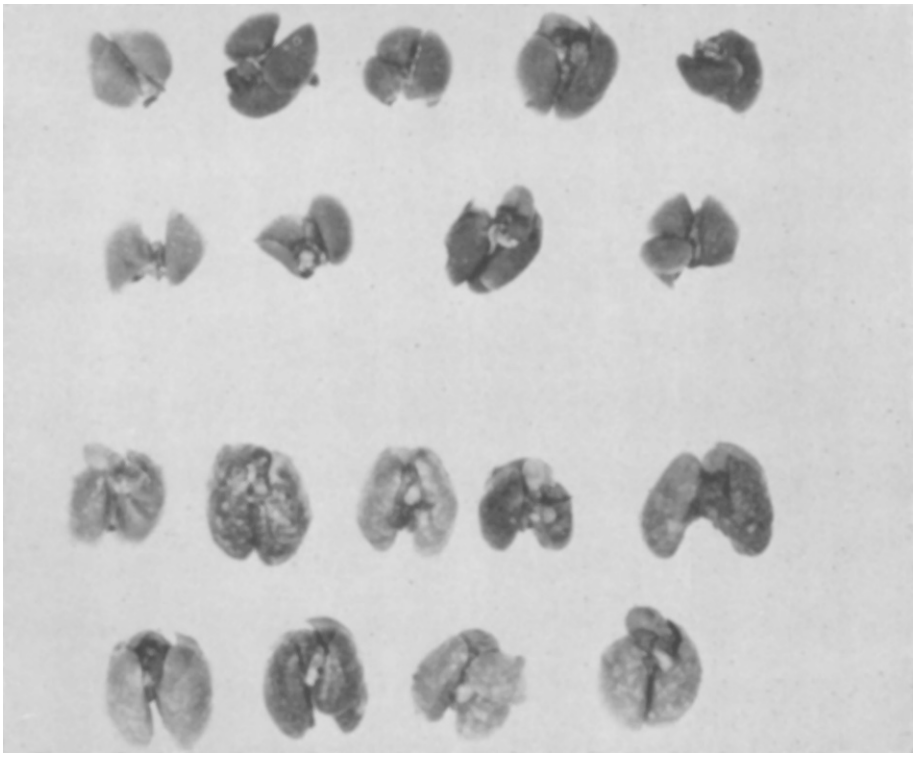

FIG. 3.
Lungs of mice infected with streptomycin sensitive strain 15. Upper 2 rows, streptomycin treated. Lower 2 rows, no treatment.

treated with a total of 3000.0 μg of streptomycin daily, given subcutaneously in 4 equally divided doses at intervals of 6 hours. Treatment was continued for a period of 35 days at which time the surviving mice were sacrificed and observed for the presence of gross tuberculous lesions. Portions of the lungs of 2 mice in each group were cultured for the presence of tubercle bacilli and the cultures obtained were retested for their sensitivity to streptomycin in the manner described previously.[2]

Results. Table I shows the results of the treatment of mice experimentally infected with streptomycin sensitive and resistant cultures of virulent human-type tubercle bacilli. Groups 1 and 5 confirm our previous report[3] that streptomycin exerts a marked suppressive effect on tuberculous infections of mice. All the mice in these 2 groups gained weight over the period of treatment and showed no gross evidence of tuberculosis upon autopsy. Groups 3, 4, 7 and 8 show clearly that not only are the streptomycin resistant cultures virulent for mice but also that streptomycin in the doses used does not influence the course of the infection.

Fig. 1, 2, 3 and 4 show the lungs of the mice. These illustrate graphically the effect of streptomycin in suppressing the infections produced by the streptomycin sensitive tubercle bacilli and the ineffectiveness of streptomycin for the suppression of infections caused by the streptomycin resistant strains.

Tubercle bacilli were reisolated in cultures from the lungs of mice from all 10 groups, though in smaller numbers from those infected with the streptomycin sensitive cultures and treated with streptomycin. The streptomycin

[2] Youmans, G. P., *Quart. Bull. North. Univ. Med. School*, 1945, **19**, 207.

[3] Youmans, G. P., and McCarter, J. C., *Am. Rev. Tuberc.*, 1945, **52**, 432.

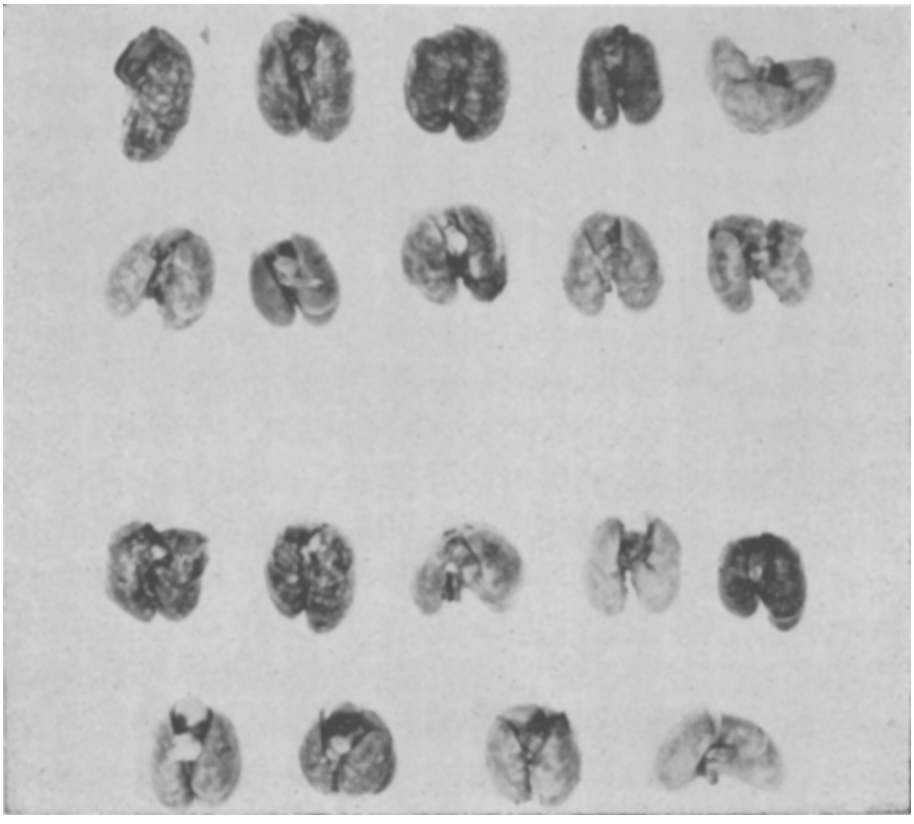

FIG. 4.
Lungs of mice infected with streptomycin resistant strain 67. Upper 2 rows, streptomycin treated. Lower 2 rows, no treatment.

sensitivity of these reisolated cultures was found to be the same as before injection into the mice.

Summary. Streptomycin resistant human type tubercle bacilli were found to be as virulent for white mice as streptomycin sensitive strains. Infection produced in mice with these streptomycin resistant cultures was not suppressed by treatment of the mice with streptomycin.

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Variation in Influenza Viruses. A Study of Heat Stability of the Red Cell Agglutinating Factor.*

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For estimating the degree of stability of a variety of materials, both biological and non-biological, it is common practice to utilize elevated temperatures in order to accelerate

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