

# The Resistance of Bacteria to Streptomycin, Especially on the Origin of Resistance.

By

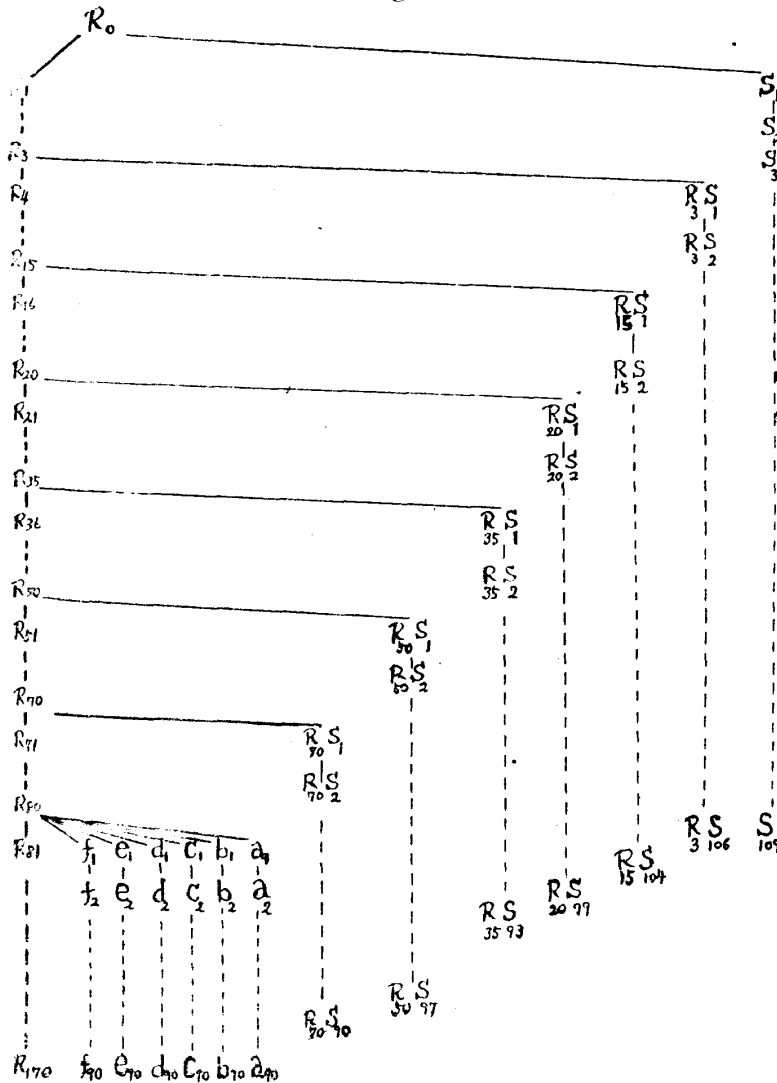
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Fig. 1.



## 1. Reduction of Resistance.

The capacity for resistance to a drug, once acquired, has usually a fairly permanent character. Is the resistance to streptomycin permanent or not? To determine the stability of the resistance the next experiments were performed. Streptomycin resistant salmonellas (Salm. ent. No. 1891, Osaka Univ.) growing on the 2.5% agar with 1,000 $\gamma$ /ml. of streptomycin were inoculated successively every 48 hours (R). After every several subcultures the resistant strains were transferred to the streptomycin free media and subcultured repeatedly (S) (Fig. I). Then the resistance of

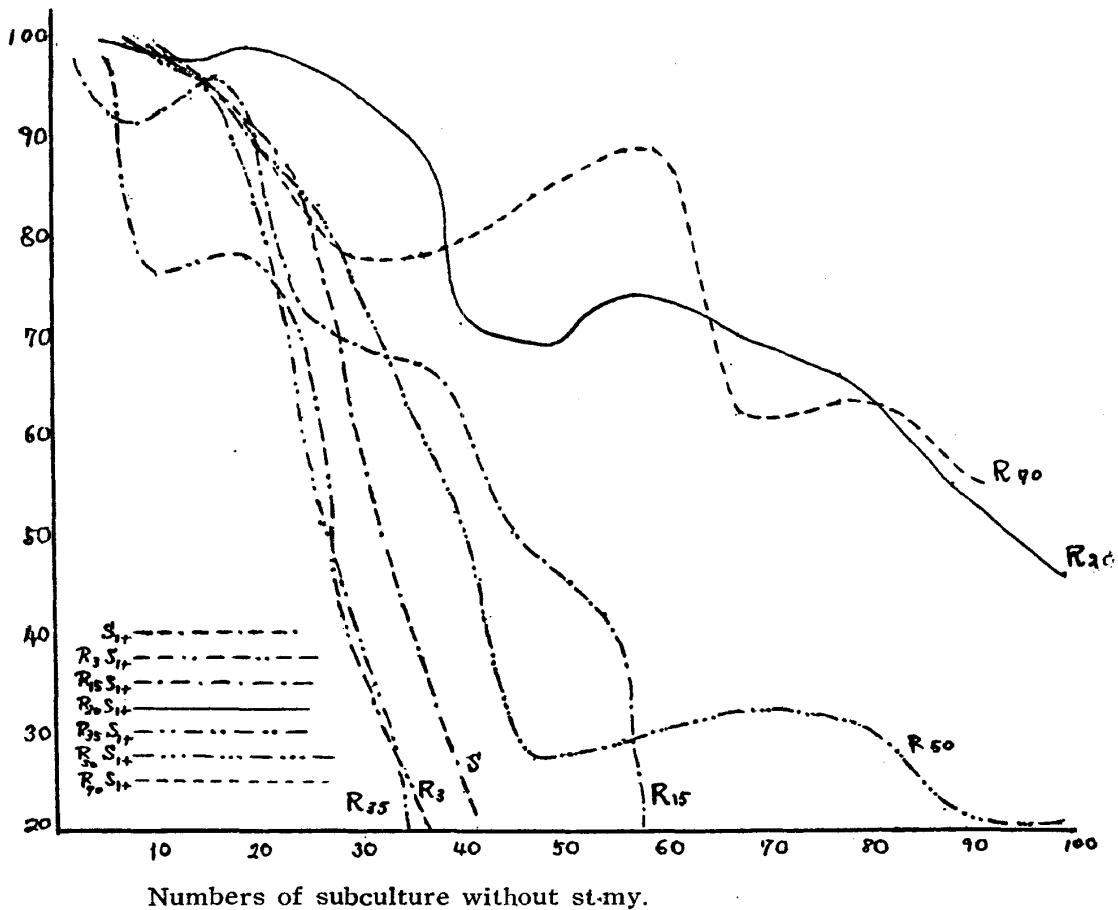
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these R and S strains was tested and compared systematically.

As shown in Fig. II almost all the strains reduced their resistance uncorrelatedly with serial numbers of subcultures containing streptomycin.

$\frac{\text{log. cell count with st.my. } 1,000\gamma/\text{ml.}}{\text{log cell count without st.my.}}$

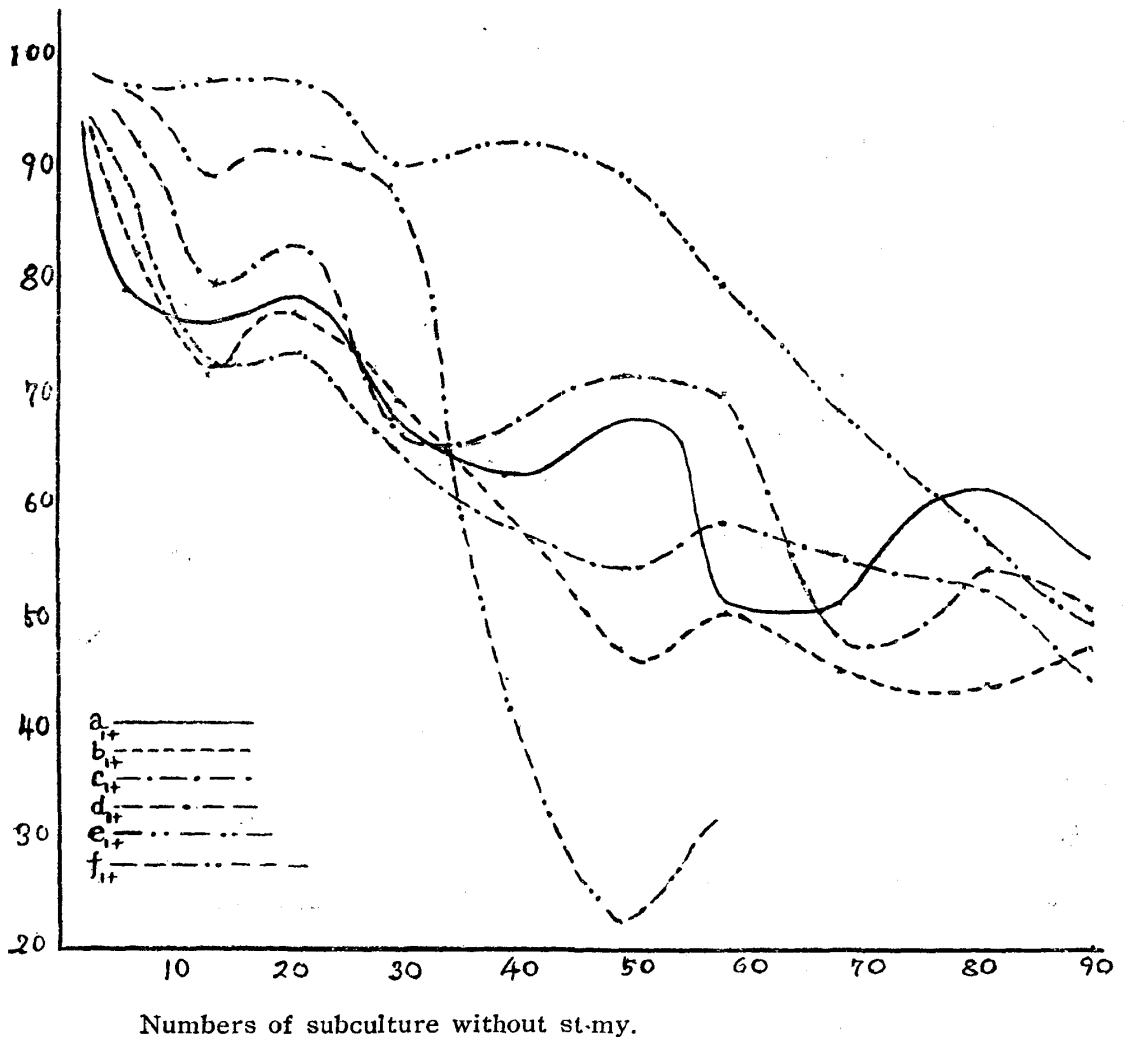
Fig. II.



Then the resistance of a few strains treated 80 subcultures with streptomycin also tended to decline through 90 subcultures without streptomycin (Fig III).

$\frac{\text{log. cell count with st-my } 1.000 \gamma/\text{ml.}}{\text{log. cell count without st-my.}}$

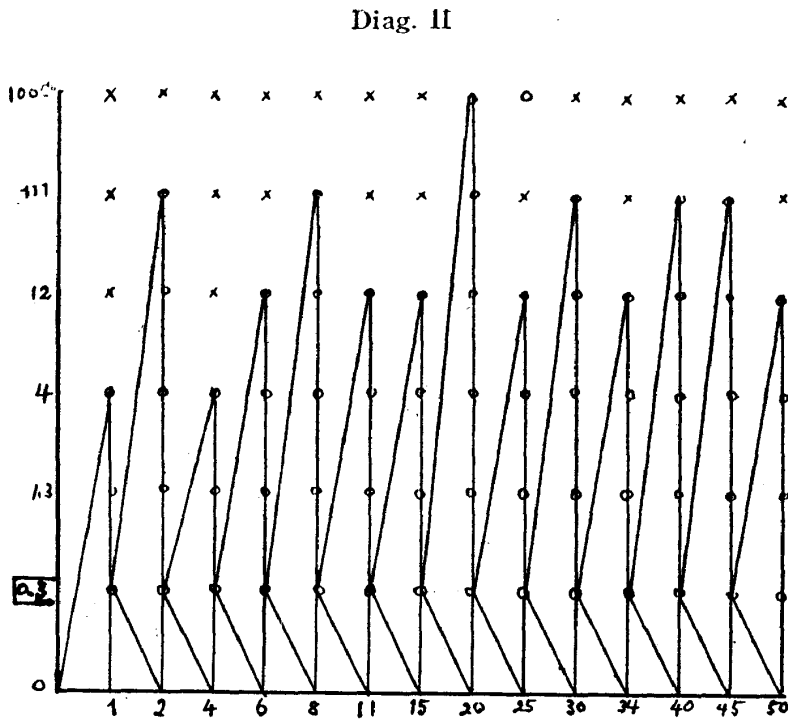
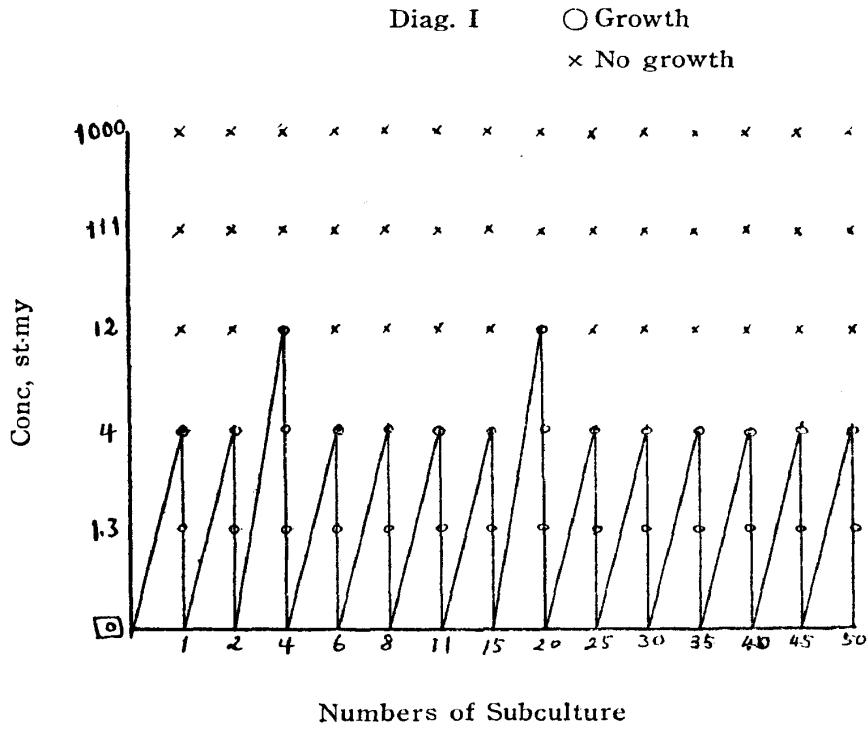
Fig III.



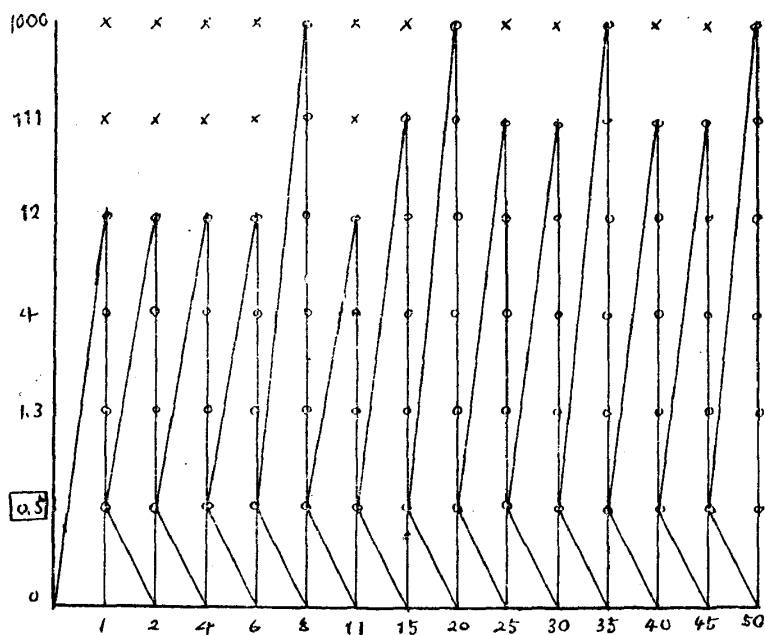
## 2. The Origin of the Resistant Strain.

The multiplication of bacteria showing increased resistance to drugs is usually assured to be the result of adaptation or mutation. To investigate this important genetical problem, we proceeded the following experiments.

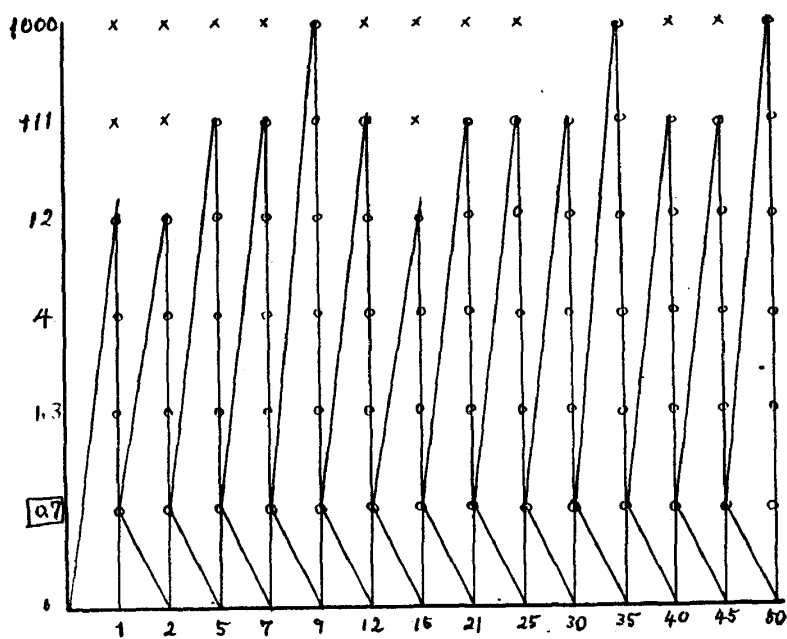
By exposing a strain of salmonellae to a range of concentration of streptomycin in a 2.5% agar plates, a striking and consistent pattern has been observed. The experiments were repetitive training by subculturing repeatedly from 0.3; 0.5; 0.7 to 1.0 $\gamma$ /ml. of streptomycin and determining the level of resistance at each subculture. The results are shown in the accompanying diagrams (1-5).



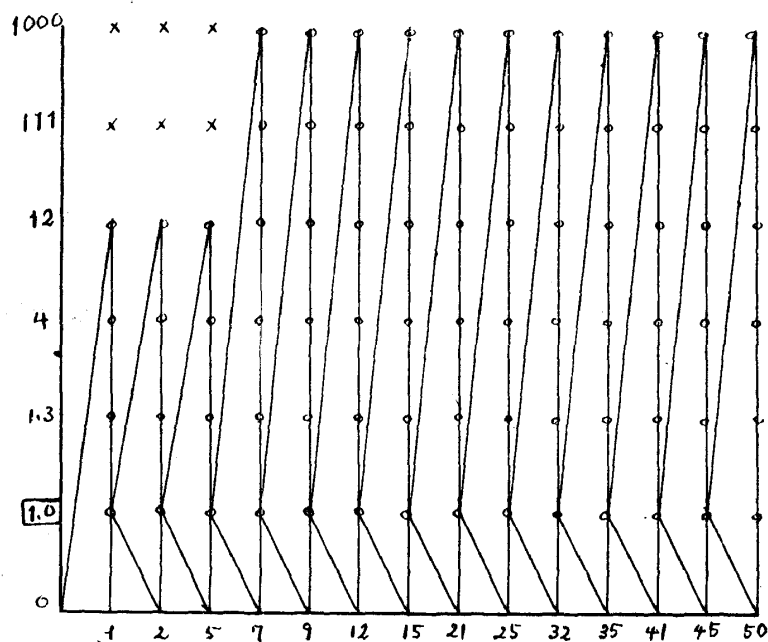
Diag. III



Diag. IV



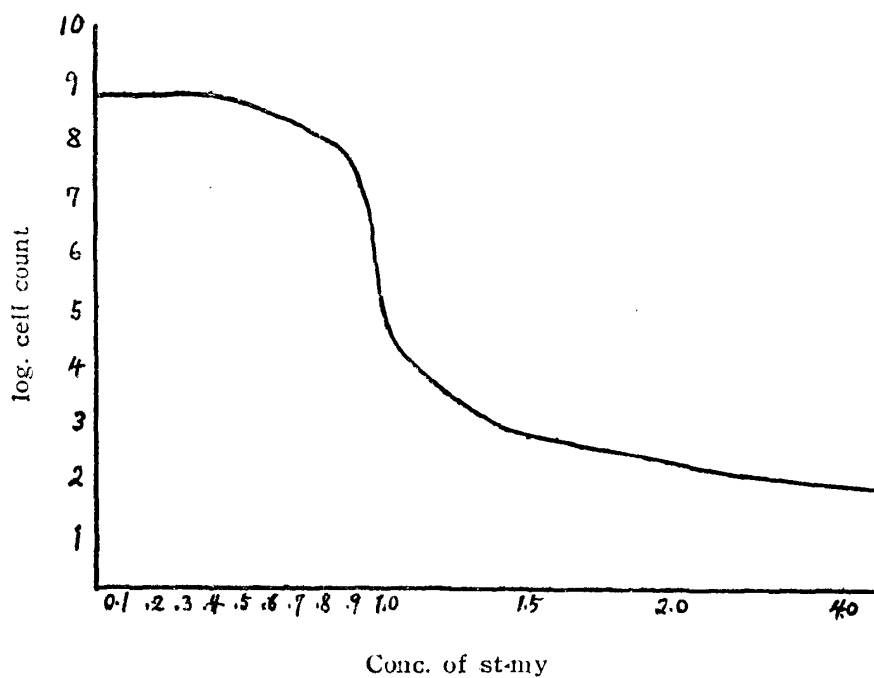
Diag. V.



The range of concentration was indicated in the diagram. All cultures incubated for 24 hours at 37°C.

Now we should point out that the sublethal dose of streptomycin to salmonellae was 0.5 $\gamma$ /ml. as shown in Fig. IV.

Fig. IV



From the result, it appears reasonable to postulate that an increase in resistance is partially due to adaptation initiated by exposure of the cells to sublethal concentration of the drugs. In addition, the results also confirmed that resistance can be reached from the lethal dosis in a few steps, indicating a mutation either occurring spontaneously, or induced by the drug itself.

#### **Summary.**

(1) The resistance of salmonellae to streptomycin tended to decline by subculture.

(2) The development of resistance to streptomycin is partially due to adaptation.

We wish to thank Prof. S. HATTORI supporting this work.

#### **References.**

- 1) WORK, T. S., and WORK, E., *The Basis of Chemotherapy*, New York, (1948)
- 2) GIBSON, M. I., *Nature*, No. 4238, p. 113 (1951).