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October 12, 1946.

Dr. J.B.S. Haldane,
Dept. of Biometry,
University College,
London, England.

Dear Prof. Haldane:

Prof. Delbruck has been kind enough to allow me to see a copy of your manuscript: 'The Statistical Theory of Bacterial Mutations.'* This paper was especially interesting because Dr. F.J.Ryan (of Columbia University) and I have been studying the reverse-mutations of biochemical mutants of bacteria, and have had occasion to attempt to estimate rates of mutation from the frequency of mutants by the general procedures described by Delbrück.

In the course of this work a mathematical problem has arisen concerning which we should like to elicit your opinions or suggestio The experiments of Luria and Delbrück revealed large differences in the number of mutants from culture to culture, the large value of the variance being ascribed entirely to the a-normal distribution resulting from clonal multiplication. It seemed possible that this variance might be the result of,in part, or might obscure,difference in mutation frequencies due to uncontrolled variations in cultural conditions. It was hoped to test this hypothesis by using double mut of bacteria, and determining, in different samples of a given cultur the frequency of reversions at each locus. Initially, instances of c incidental reversion were looked for, without success (as predicted the theory that they were independent events, and from the individua reversion rates of ca. 10^{-8}.) Then data were accumulated from which hoped to be able to draw inferences concerning the correlation of mu

in cultural conditions, which were responsible for the variation in mutant frequencies, and if these influences were not locus-specific there should be found correlations between the reverse-mutant frequencies from one culture to another.

The experiments are in accord with the findings of Luria and Delbrück and large variances are found from culture to culture. A superficial inspection of the correlation experiment data also seems to imply that there is no correlation. However, we would like to have objective, well-founded statistical techniques for this problem, and we do not feel that they are available. A rank-order comparisn was thought to have some validity even for distributions lik this; while its application indicated a low order of correlation, we are still not sure of its justifiability.

Since we have since prepared (by successive irradiation) mutants at several loci, the problem can be generalized to an n-th order comparison.

Your consideration of this puzzle would be highly appreciated. We should also be very much obliged for an exchange of publications relevant to bacterial genetics and particle enumeration.

I might add parenthetically that the independent occurrence of mutations at several loci. which seems to be borne out by these experiments, is an important postulate upon which the validity of our conclusions that recombination of genes may occur in bacteria is based.

With best regards, Respectfully yours

Joshua Lederberg.