CONTRIBUTION TO THE MANNER OF SPREAD OF MOUSE
TYPHOID INFECTION.

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In the preceding paper we state that the spread of mouse typhoid
in a given mouse population is determined by three factors, or vari-
bles; namely, the spacial and quantitative distribution of the bacilli,
the virulence of the microorganism, and the susceptibility of the host.
That the last two factors are concerned in this process has been shown
by the experiments in which the bacilli remained virtually of constant
virulence while the susceptibility of the mice varied considerably.
In the present paper we propose to describe experiments dealing more
specifically with the factor of bacillary distribution under circum-
stances in which the mice were exposed to infection through the normal
channels and without artificial instrumentation. Moreover, using
the experimental results recorded in this paper and the preceding
one as a basis, we have compared our standard control curve with
the epidemic curve as given by Amoss for mouse typhoid epizootics
and, having discovered a striking correspondence between them,
have suggested an explanation of the manner in which the epidemic
curve is produced.

Spacial and Quantitative Distribution of Bacilli.

In the experiments already reported each mouse was given a fixed
and constant amount of the routine culture of mouse typhoid bacilli
(Bacillus pestis cavia) per os through a specially devised tube. In the
tests now to be described, contact experiments were arranged in such
a manner that healthy mice and mice inoculated by means of the tube

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*per os* were brought together in a way calculated to vary the concentration of the available infecting bacilli.

**Experiment 1.**—100 normal mice, bred at The Rockefeller Institute, weighing 16 to 18 gm. each, were assembled as follows: Series A consisted of 20 jars containing 2 mice each; Series B consisted of 10 jars containing 6 mice each. Of Series A, 1 mouse in each jar, and of Series B, 5 mice in each jar received by stomach tube 0.5 cc. of an 18 hour heart's blood broth culture, diluted 1:100. The activity of the culture was controlled by means of 20 mice in separate jars, each of which was given a similar dose.

![Text-fig. 1. Mortality curves of Series A, Experiment 1.](image)

In this experiment each jar of Series A contained 1 inoculated and 1 uninoculated mouse, while in Series B each jar contained 5 inoculated and 1 uninoculated mouse. It was therefore probable that the single contact mouse per jar in Series B would be exposed to and hence would ingest a larger number of bacilli voided by the 5 inoculated...
mice than would the single contact mouse in Series A, in which only 1 inoculated mouse shared the jar. Text-figs. 1 and 2, which reproduce the mortality curves of the two series, exhibit the different results attained which are in conformity with the prediction.

The figures bring out the strikingly different effects induced by mere dosage of the bacilli alone. Thus in Series B, in which the ratio of inoculated to uninoculated mice was 5:1, the mortality curve of the contact mice agrees closely with that of the control curve based on the 20 mice each of which was given a fixed dose of the bacilli; while in Series A, in which the ratio was 1:1, the mortality of the contact mice is almost negligible. The results of the two tests are so impressive that they may be taken as indicating that with a homogeneous mouse stock the factor of dosage alone, conditioned only upon the quantity of bacilli available being large, is sufficient to induce massive infection leading to death, while conversely when the available dosage is small it is insufficient to produce this severe effect.

The next experiment was planned in a way to enable us to show the influence of crowding upon a series of mice all of which had been given per os a uniform dose of mouse typhoid bacilli.

Experiment 2.—100 mice from the breeding room, weighing 16 to 18 gm. each, were assembled as follows: 20 mice were placed in each of 3 separate cages measuring 14 by 14 by 14 inches and designated A, B, and C. 5 mice were placed in each of 4 cages (battery jars) measuring 8 by 10 inches. 1 mouse was placed in each of 20 battery jars of the same dimensions as the preceding. These last single mice served also as controls for Experiment 1. Each mouse of the various series contained in the several jars received per os by tube 0.5 cc. of an 18 hour heart's blood broth culture, diluted 1:100. This culture was also used in Experiment 1.
Text-fig. 3 shows that the mortality in Cages A, B, and C, in which the crowding of the mice was greatest, was higher than in the jars in which the crowding was less; and the mortality was least among the isolated control mice.

The explanation of the differences is obvious; the mice in Cages A, B, and C received not only a fixed initial dose of the culture but large additional quantities eliminated by the sick mice with the dejecta and through the devoured dead companions. In this way even the more resistant mice become infected and tend to succumb. From all of which it may be concluded that degree of distribution or dosage of the bacilli is a determining factor in the increased death rate.

Comparison of Standard Control and Experimental Epidemic Curves.

Experiments, carried out on 10 series of mice from The Rockefeller Institute breeding room totaling 520 individuals, have shown that when a given dose of mouse typhoid bacilli is administered per os, the mortality curve is, generally speaking, a constant one. We refer to this curve as the standard control curve.

In order to compare the standard curve with the curve based on epidemics of mouse typhoid, we plotted the former with coordinates similar to those employed by Amoss in recording the mortality in experimentally induced mouse typhoid epidemics. The resulting curve parallels closely Amoss' experimental epidemic curves which followed the introduction of a fresh population into an infected community. This parallel is shown in Text-fig. 4. Hence the question presents itself whether the factors accounting for the standard curve may not also explain the epidemic curve. Generally, of course, it is unwise to relate causally independent series of phenomena merely because they may be described by the same type of curve. In this instance, however, in which conditions are so closely allied and in which we are comparing controlled phenomena with like uncontrolled phenomena, a similar causal relation on the basis of similarity of curves seems more justifiable.

Our experiments show that the standard control curve arises from the spacial and quantitative distribution factor; that is, from the artificial injection per os of mouse typhoid bacilli or from conditions
described in this paper (Experiment 1). This being the case, it may be inferred that the epidemic curve is initiated by a like distribution factor acting upon a susceptible population. Furthermore, the character of this standard control curve represents an equilibrium between microbic virulence and host susceptibility, and since it is found that under the conditions of the experiments virulence remains constant while susceptibility varies, it would appear that variation in the form of this curve results from differences in susceptibility of the mice. From these considerations we have concluded that the form of the curves given by Amoss for experimentally induced epidemics of mouse typhoid depends upon the degree of susceptibility of a mouse population simultaneously exposed to a fixed and infectious dose of mouse typhoid bacilli.

In using the standard control curve to explain the mortality figures in a spontaneously occurring epidemic of mouse typhoid, we are on less sure ground since the conditions of exposure may be less constant than those existing in the experimental epidemics, whence it follows
that the curve will be irregular and rise and fall with the fluctuation of the spacial distribution of the bacilli as well as with the varying individual susceptibilities of the mice.

The influence of the distribution factor is exhibited, in our opinion, by Topley's\textsuperscript{1} studies in which many mice were kept together in a single large cage to which fresh increments were added from time to time. We believe that the quantitative distribution factor in these experiments was affected by the care given the cage (removal of refuse, etc.), by the number and individual quality of the mice, and by the death rate. A high death rate among a recently added population indicated great concentration of the bacilli; a low death rate the reverse condition. In other words, Topley's curves can be accounted for without assuming a change in infecting power of the mouse typhoid bacilli.

Similarly the experimental results of Amoss\textsuperscript{2} in which the mice were assembled in groups of 5 and 10 can be explained on the basis of the spacial and quantitative distribution of the bacilli alone, in the first instance by the attendant and in the next by the number of mice acquiring and succumbing to infection.

CONCLUSION.

The experiments reported in this paper and in the preceding one\textsuperscript{1} indicate that with a given susceptible mouse population and a certain strain of mouse typhoid bacilli the sporadic and epidemic prevalences of mouse typhoid are determined by the spacial and quantitative distribution of the bacilli.

Under circumstances in which the entire mouse population is so exposed as to be in direct contact with an infecting dose of the mouse typhoid bacillus, the nature of the resulting mortality curve depends upon the quality of susceptibility of the individuals composing the population.