THE SPREAD OF BACTERIAL INFECTION[1].

THE POTENTIAL INFECTIVITY OF A SURVIVING MOUSE-POPULATION, AND THEIR RESISTANCE TO SUBSEQUENT EPIDEMICS OF THE SAME DISEASE.

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(With 2 Charts.)

In a previous communication (1921) experiments have been described showing the effect produced by continuously adding normal mice to a cage, the population of which is infected with bacilli of the group which includes *B. gaertner* and *B. suipestifer*. It was seen that under these circumstances the spread of infection progresses in a series of epidemic waves, and that the survival-time of any batch of mice varies according to the period at which they are introduced to the cage. It was further shown that, if such regular and continuous addition of susceptible animals be persisted in over long periods of time, all the mice will eventually succumb, while, if the addition of new individuals be discontinued, the epidemic will eventually subside, leaving a proportion of survivors who may remain in apparently good health over a considerable period.

In one experiment, in which an infected population was thus kept isolated for 77 days after the last addition had been made to the cage, the 15 survivors were killed and examined post-mortem. From nine of them the organisms which caused the epidemic were recovered. It therefore seemed probable that a condition of equilibrium had been attained between the parasites and their hosts, which might be maintained indefinitely so long as the surviving population was kept isolated from susceptible individuals of the same species. The experiments outlined in the present report were undertaken in order to ascertain how this equilibrium would be affected by the addition to the cage of a relatively large number of normal animals.

Two experiments have so far been carried out on mice infected with *B. gaertner* and *B. suipestifer*. It has already been noted that infection with either of these organisms produces a disease which is indistinguishable from that produced by the other, and that if an epidemic be started by feeding mice on a culture of *B. gaertner*, *B. suipestifer* may be isolated from a high proportion of the animals subsequently dying, either alone or associated with the former organism.

[1] A Report to the Medical Research Council.

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Experiment I.

This experiment was carried out on the survivors from an epidemic which has been recorded in the communication already referred to. The original experiment was commenced on May 18th, 1920. The epidemic was well under way by the latter half of June, and the addition of normal mice was discontinued on July 24th. Until that date three normal animals had been daily added to the cage. The course of events from July 2nd onwards is recorded in Chart I. It will be seen that the epidemic had practically come to an end by the middle of September, though one death occurred on the 28th of that month, on which day there were five survivors. No further deaths occurred up to November 12th, and on that date 20 normal mice were introduced into the cage. A study of the chart, in which every shaded square corresponds to the death of one mouse, while the death of each survivor from the earlier epidemic is indicated by an unshaded square marked with a dot, will show that a small group of deaths occurred between November 18th and December 6th. During this period none of the survivors succumbed. There was no satisfactory evidence however that the deaths were the result of the infection under consideration. This lack of evidence may well be due to the fact that several of the dead mice were eaten by their companions, but the cause of death must be regarded as undetermined. For more than a month after December 6th no death occurred in the cage; but on January 12th another outbreak commenced, which resulted in the death of 16 of the 19 surviving mice during the following 31 days. The three remaining animals died during the following six weeks, and the last to succumb was one of the survivors from the original epidemic. Of the 25 mice which died after the addition of the fresh susceptibles, four were eaten by their companions, in two the cause of death was undetermined, while from the remaining 19 *B. suipestifer* was isolated, usually in pure culture. It may be noted that the great majority of the mice dying during the original epidemic yielded cultures of *B. gaertner*, while *B. suipestifer* was isolated from relatively few animals. This variation in the serological type of the prevalent organism in the two outbreaks may well have introduced a disturbing factor.

It appears that the addition of a considerable number of susceptible individuals to a population which has survived an epidemic of disease, leads to the outbreak of a fresh wave of infection. During this second epidemic some or all of the survivors themselves may succumb, but the newcomers suffer first and more severely. This point would be more satisfactorily brought out in this experiment if we could be certain of the cause of the earlier group of deaths. It is however clearly indicated in the experiment next to be described.

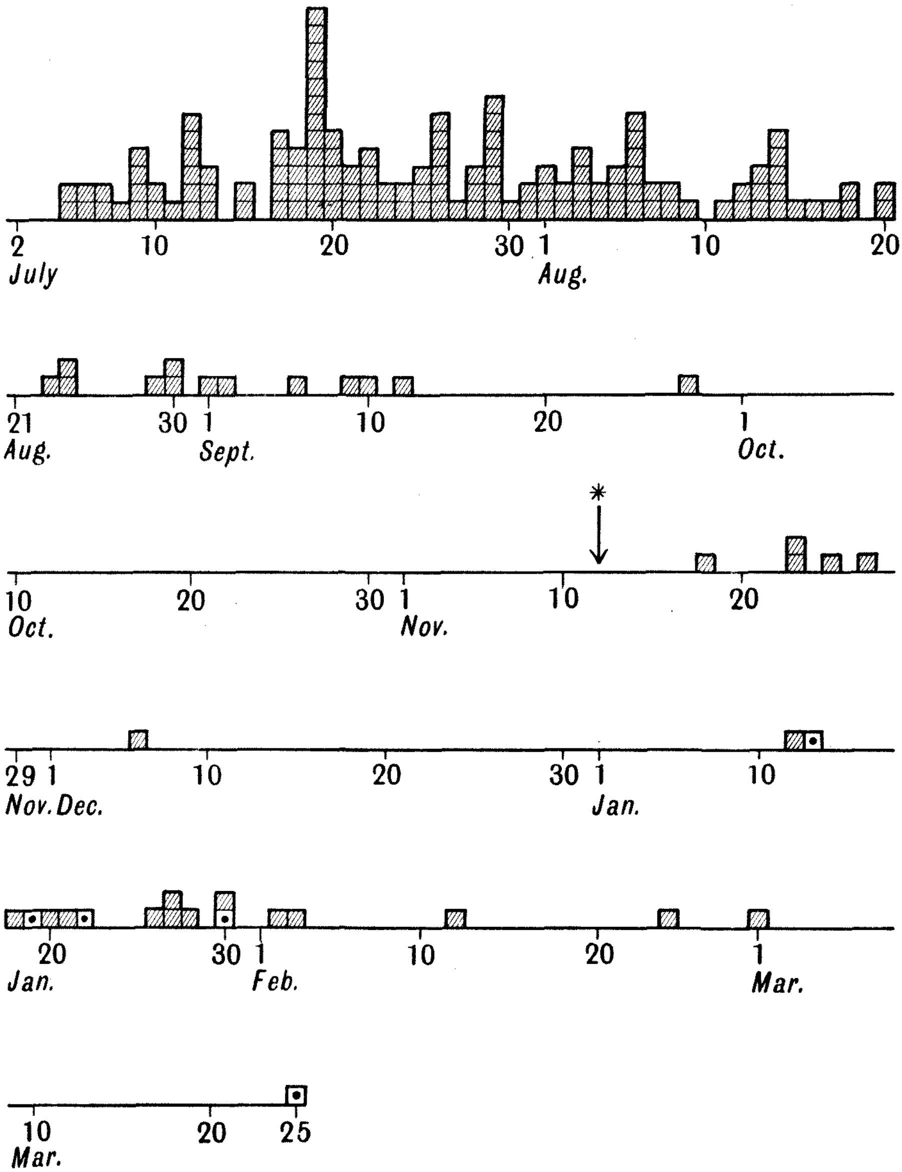

Chart I.

* 20 normal mice added.

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Experiment II.

In this experiment advantage was taken of an outbreak among the normal stock, which was probably caused by an accidental spread of infection from the experimental cages. Deaths began to occur on August 14th, 1920, and between that date and August 23rd 26 deaths took place in a number of cages placed together in a large enclosure. From nine of these mice *B. suipestifer* was isolated, from eight *B. gaertner*, and from three both types of organism. From the remaining six mice no member of this group was recovered, but the evidence was strongly in favour of their having succumbed to the same infection. On August 23rd there were 124 survivors in these cages. Forty were living in four cages in each of which deaths had occurred. The remaining 84 were distributed among eight cages which had shown no evidence of infection; but since there had been ample opportunity for cage-to-cage infection within the enclosure it is unlikely that they had altogether escaped. These 124 mice were now placed together in a large experimental cage. The subsequent course of events is shown in Chart II which is constructed on the same principle as Chart I. It will be seen that 111 mice succumbed to the epidemic between August 23rd and October 14th. Thirty of these could not be examined post-mortem since they were eaten by their companions. From 13, which were examined post-mortem, no organism of the gaertner-suipestifer group was isolated. From the remaining 68 mice cultures of *B. suipestifer* were obtained from the heart or spleen, or from both situations, usually in pure culture.

During this period two mice had been accidentally killed, so that on October 14th there were 11 survivors. By November 22nd no further deaths had occurred, and on that date 44 normal mice were added to the cage. Only two deaths occurred between November 22nd and January 5th. One of these animals was eaten: in the other the cause of death remained undetermined. On January 6th one mouse died from a typical *B. suipestifer* infection. Another died on the 14th, and a few days later a definite epidemic was established. Between January 14th and February 16th 39 mice died, while during the following month four of the remaining animals succumbed. The other nine mice remained in apparently perfect health for another month, when the experiment was discontinued. From 42 of the 45 mice, which died subsequently to the addition of the fresh susceptibles, *B. suipestifer* was isolated post-mortem. One mouse was eaten by its companions, and in two the cause of death was undetermined. As will be seen from the chart, 24 of the newcomers met their death before the first of the survivors from the original epidemic succumbed to the fresh outbreak of infection. At the time when the experiment was discontinued 39 of the 44 newcomers had died, while four of the 11 survivors from the original epidemic also survived the second.

In these, as in all similar investigations, the value of any conclusions which may be drawn depends largely on the consistency of the evidence obtained in a considerable number of experiments; and the results of those reported here

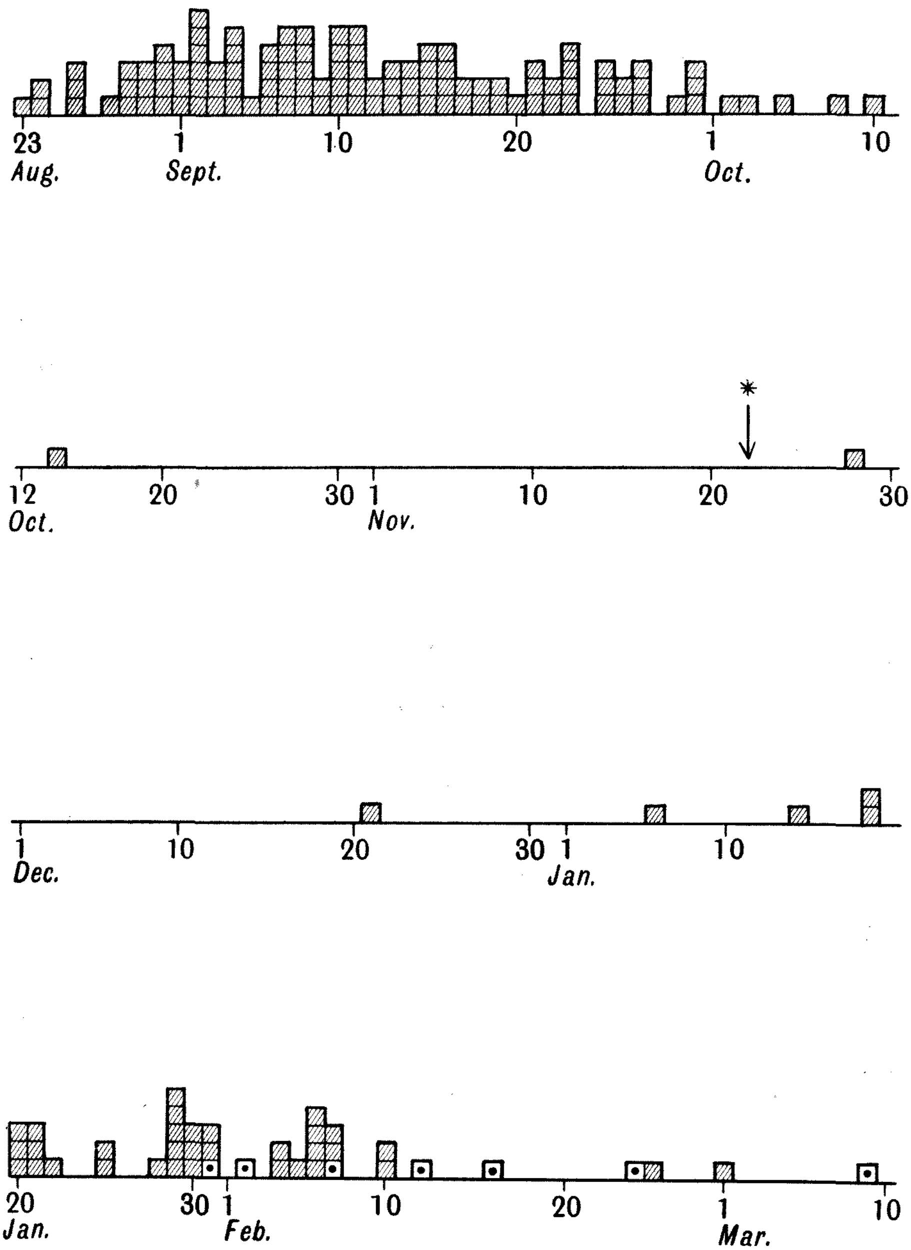

Chart II.

* 44 normal mice added.

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must clearly be checked by others carried out along similar lines. Such experiments, however, involve observations carried out over many months, while the course of events in those described above accords well with the facts already elicited.

In the report referred to above it was concluded from the evidence obtained that, if a population which is subjected to an epidemic of bacterial infection be kept isolated, a variable proportion will survive, and that the greater number of these surviving individuals have not escaped infection, but have successfully resisted it. It was suggested that a possible explanation of the continued existence of these survivors in apparent well-being was the establishment of some equilibrium between parasite and host. Such an equilibrium would probably depend upon the infectivity and distribution of the parasite, and the relative immunity of the hosts, either acquired as the result of a mild or atypical infection, or natural to the individuals concerned.

The experiments here reported have shown that such a surviving population may live together in apparent health for a considerable period; and this fact has been confirmed by the observation of several other experimental epidemics. It is further shown that such surviving populations, the individuals of which are apparently non-infective towards one another, possess a quite definite infectivity for fresh susceptibles which are subsequently added to the cage. The considerable period, which elapsed in each experiment between the introduction of these susceptibles and a definite outbreak of the infection concerned, suggests that we are not dealing with an infection of uniform intensity, passed from a healthy carrier to one or more susceptible individuals, but that some process is set in motion, which results in an increase in the infectivity of the parasite, this in its turn giving rise to a fresh wave of mortality among the cage-population.

The fate of the survivors from the original epidemic is of especial interest. It will be seen that they tend definitely to outlive the newcomers to the cage. The fact that these mice, which are immune to the risk of infection from their original companions and able to withstand the earlier stages of the fresh spread of infection among the new arrivals, themselves succumb during the later stages of the epidemic, points strongly to the conclusion that the fresh wave of mortality is associated with a definite increase in the infectivity and virulence of the parasite. Such a variation has been suggested in previous communications (1919, 1921) as an essential factor in the epidemic spread of bacterial infection.

If it be a general law that a state of equilibrium is established in a population which has passed through an epidemic of bacterial disease, rendering the individuals immune to existing conditions, and even to the earlier stages of a fresh spread of infection, but leaving them potentially infective to a second population which has not been subjected to a similar process, we might find an explanation for many puzzling facts in human and animal epidemiology. The evidence is as yet too slight to justify an elaboration of this aspect of the subject, but one instance may perhaps be noted.

The influenzal epidemics of remote islands, and their apparent association with the arrival of a ship from foreign parts, have long formed a fascinating subject for speculation. Hirsch (1881), who it will be remembered sums up against the infectivity of this disease, thus concludes his relation of such outbreaks: "The fact itself can hardly be doubted; while the striking thing appears to me to be that the strangers themselves, in all the cases, have remained exempt or almost exempt from the epidemic."

CONCLUSIONS.

So far at least as the spread of enteric infection among mice is concerned, the experiments here described suggest that:

(1) A population which has passed through an epidemic of bacterial infection may, when completely segregated, survive for considerable without any fresh outbreak of the disease in question.

(2) In spite of their apparent freedom from the disease, such survivors are potentially infective towards fresh susceptibles of their own species.

(3) Should a fresh outbreak of the disease occur through the accumulation of such susceptible individuals, the relative immunity of these survivors will carry them through the earlier phases of the new epidemic, but they will tend to succumb during its later stages.

I should wish again to express my indebtedness to my colleagues Dr H. B. Weir and Dr G. S. Wilson for their constant help in these investigations.

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