THE SPREAD OF BACTERIAL INFECTION; GROUP-TO-GROUP INFECTION.

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(*A Report to the Medical Research Council.*)

(With 6 Charts.)

The results obtained by one of us in experiments already reported (Topley, 1919, 1921 *a* and *b*, 1922 *a* and *b*) and those recorded by Flexner, and his co-workers in America (Flexner 1922, Lynch 1922, and Amoss 1922 *a* and *b*) show clearly that the addition of susceptible mice to others, among which enteric infection is endemic in the sense that occasional deaths are occurring from this cause, or which have survived through a considerable and recent epidemic wave, is almost invariably followed by a new outburst of disease.

It is of interest to investigate the effect of varying the manner in which the addition of the susceptible to the infective material is carried out. The results so far recorded show that epidemic spread of infection follows the addition of susceptible to infective mice, whether this addition be carried out (*a*) at one step, (*b*) by the daily addition of small numbers of susceptibles, continued over a considerable period, or (*c*) by additions carried out irregularly and at very varying intervals. It will be noted that a common feature of all these methods of addition is that the added mice remain, until their death, as a part of the cage-population; which rises in number until deaths begin to occur and then decreases if no further additions be made, or fluctuates according to the relation between the subsequent additions and deaths.

Infection might clearly pass from individual to individual, or from group to group, in another way. Infective animals might transmit the parasite concerned to susceptible members of their own species, which might then become separated from the original source of infection, but, on coming into contact with other susceptibles, might pass on the infection to them; and this process might conceivably continue *ad infinitum*, each small group receiving infection from one previously infected, and passing it to another, hitherto free from the disease in question. In this case there would be no accumulation of a considerable population, composed of mice of varying grades of infectivity on the one hand, or of susceptibility or resistance on the other. Each group would be exposed to the risk of infection for a limited time, and would subsequently have an opportunity, over a period similarly limited, of passing on any infection which it might have acquired.

The experiments here recorded were planned to test the possibility of transmitting infection from group to group in this way.

Experiment 1. Five mice were taken from a cage in which an epidemic of infection with *B. enteritidis* (Aertrycke) was slowly subsiding. To them five normal mice were added, and the ten animals were allowed to remain together for three days. They were then separated into the two original groups, and kept segregated for three days longer. To the second group were then added five more normal mice, which were separated after three days' contact, and the process was continued as shown in Chart I, each group being in contact for three days with the group preceding it, three days in isolation, three days in contact with the group succeeding it, and then in isolation until the mice of which it was composed died or were killed and examined.

Each group was observed for six weeks, from the date on which it was first exposed to the risk of infection. The surviving mice were then killed and examined post-mortem, cultures being taken from the heart and spleen in each case. Each column in the chart corresponds to one such group, each square to a single mouse. The fate of each mouse is recorded in the manner

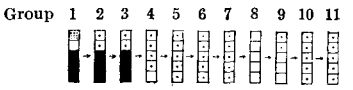

Chart I.

■ = died of enteric infection.
▣ = died from pasteurellosis.
□ = died, but no infection recognisable P.M.*
⊡ = killed 6 weeks after exposure to risk of infection—apparently healthy—and P.M. nil.

indicated in the footnotes. The time-relations are not recorded, either with regard to the intervals between contact and separation of the groups, or to the time-period between exposure to infection and death of individual mice. The inclusion of these details would make the charts both large and complex, and the essential points can be better recorded in the text. The three deaths from enteric infection which occurred among the mice of Group 1 took place 7 days, 23 days and 35 days respectively after this group was added to Group 2. The three enteric deaths in Group 2 occurred 16 days, 23 days and 31 days respectively after the mice of this group were added to Group 1. The three enteric deaths in Group 3 took place 14 days, 18 days and 24 days respectively after this group was added to Group 2. The fact that deaths may occur at these relatively long periods after exposure to risk of infection makes it somewhat difficult to know when an experiment may safely be terminated, as will be apparent later. Two other points may be mentioned which are peculiar to this experiment. One mouse in Group 1 died, as recorded in the chart, from pasteurellosis. No death from this disease had occurred in the cage from which this mouse came, and there was no apparent passage of the infection from this mouse to others during the course of the experiment. The

* P.M. stands for post mortem throughout.

https://doi.org/10.1017/S0022172400031466 Published online by Cambridge University Press

mice which died from enteric infection in Groups 1 and 2 yielded pure cultures of *B. enteritidis* (Aertrycke) from the heart and spleen, so far as could be estimated from the routine examination of three colonies from the plate from each source. The three mice which died in Group 3 yielded pure cultures of *B. enteritidis* (Gaertner). This is almost the only example we have met with of the substitution of the Gaertner for the Aertrycke type in such experiments, although the reverse change has been frequently met with as already recorded.

Experiment 2 is recorded in Chart II. The four mice forming Group 1 were survivors from a considerable epidemic of enteric infection. They were known to be carriers of *B. enteritidis* (Aertrycke), this organism having been cultivated from their faeces on several occasions. There is, therefore, a strong probability that, had they been added to a large number of susceptibles kept in a single aggregate, an epidemic of the usual form would have resulted. The periods of contact, separation and isolation differed in this experiment from those which were observed in Experiment 1. Each group was in contact with the

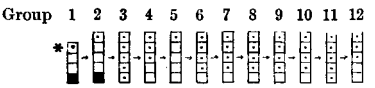

Chart II.

* This mouse died of enteric infection on the 44th day.

■ = died from enteric infection.

□ = died, but no known infection recognisable. P.M.

⊡ = survived more than 42 days.

preceding group for 7 days. It was then removed and immediately placed in contact with the succeeding group, separated again after another 7 days, and then kept in isolation. The mice, in this experiment, were not killed after a lapse of 42 days, but were retained for another purpose. The record is, however, carried to the 42nd day for the sake of uniformity. As noted in the chart, one mouse from Group 1, recorded as surviving for more than 42 days, succumbed to enteric infection on the 44th day. With this exception, no mouse showed any evidence of such infection, though all were actually observed over many months.

Experiment 3 was started with five mice (Group 1) similar in every way to those constituting the first group of Experiment 2. The only difference in technique was that the period of contact between each group and the group

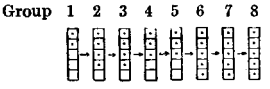

Chart III.

□ = died. P.M. nil.

⊡ = survived more than 42 days (except batch 8, which were only observed for 21 days).

succeeding it was 21 days instead of 7. As in Experiment 2, no interval elapsed between the separation of a given group from its immediate precursor and its addition to the group next following. The results are recorded in Chart III.

Experiments 4, 5, *and* 6 (Charts IV, V and VI) were carried out by adding five mice, which constitute Group 1 in each of the corresponding charts, to a large cage in which a long-continued epidemic of pasteurellosis was under way, but in which occasional deaths were occurring from enteric infection. After a few days in the cage, the mice were removed and placed in contact with the

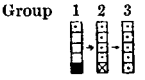

Chart IV.

■ = died from pasteurellosis.
□ = died. P.M. nil.
⊠ = died and eaten.
⊡ = killed 6 weeks after exposure to risk of infection. Apparently healthy. P.M. nil.

mice forming Group 2. After a similar interval Group 2 was separated from Group 1 and placed in contact with Group 3, and so on. No interval elapsed between the successive periods of contact. In Experiment 4 the mice of Group 1 were in the infected cage for 7 days, and this was also the period of contact between the successive groups. In Experiments 5 and 6 the period of contact was shortened to 4 days, the other conditions being unaltered.

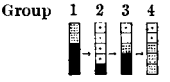

Chart V.

■ = died from pasteurellosis.
▦ = died from enteric infection.
□ = died. P.M. nil.
⊡ = killed 6 weeks after exposure to risk of infection. Apparently healthy. P.M. nil.

A few points may be recorded with regard to Experiment 5. The deaths from pasteurellosis among the mice of Group 1 occurred 3, 6 and 18 days after exposure to infection, those from enteric infection occurred after the lapse of 25 and 39 days. The death from pasteurellosis in Group 2 occurred 26 days

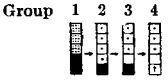

Chart VI.

■ = died from pasteurellosis.
▦ = died from enteric infection.
[t] = abscess in left lumbar region. Cultures: *B. proteus*.
⊡ = killed 6 weeks after exposure to risk of infection. Apparently healthy. P.M. nil.
□ = died. P.M. nil.

after exposure to risk, and 12 days after Group 3 had been separated from Group 4. The deaths in all other groups occurred considerably later, so that at the time when Group 4 was placed in isolation there was no evidence of any spread having occurred. In the light of previous experience the experiment was stopped at this point. This was somewhat unfortunate, since the final

results afford the only evidence of any continuous spread of infection from group to group.

The general trend of the evidence is, however, sufficiently clear. The exposure of susceptible mice to the risk of infection, when carried out in the way indicated, is followed by a sequence of events differing widely from that observed in other experiments, in which the conditions of contact were different. There is, in four out of the six experiments, evidence of spread of infection from Group 1 to Group 2. If, as is logically correct, we regard Group 1, in Experiments 4, 5, and 6, as the first exposed group rather than as the infecting group, then in only one experiment (Exp. 3) is there an entire absence of spread. This spread, however, in all cases soon ceases, and in only one experiment does it reach beyond the third group exposed to risk.

DISCUSSION.

In what relevant ways do the conditions in these experiments differ from those obtaining in the experiments previously reported? There are at least two points of difference which may well be significant. In these experiments the mice of a given group can only be infected by the mice of the group immediately preceding it. In experiments where additions are made without subsequent separation, the mice of any group will also be subjected to the risk of infection from the surviving mice of all preceding groups. The opportunity of transmitting infection afforded to any given mouse is also very different. In the present series of experiments this is limited to a period varying from 3 to 21 days, after which no further mice, except those of the same group, can be infected. The possible importance of these differences is obvious. If the period of infectivity of any given mouse is usually a short one, limited to some definite phase of infection, the separation of successive groups after an arbitrary interval may prevent contact at the critical period. In this connection attention has been drawn, in an earlier report (Topley, 1919), to recorded observations in connection with infection in man, which suggest that such phases of maximal infectivity do indeed exist. If, on the other hand, certain individuals remain infective over long periods owing to some factor which modifies the more usual course of events, or if an individual, after passing from the infective to the non-infective condition, may become infective again owing to some recrudescence of bacterial activity, then the method of limiting the path of infection to spread from group to group will clearly reduce the chances of the successful propagation of the disease in question to an unknown but probably considerable degree.

The factor concerned will, in a sense, be a variation of dosage; the importance of which has been emphasised by Amoss (1922 *b*); but it may, perhaps, be more truly regarded as a variation in the risk of infection run by any given mouse, owing to the fact that intermittently or continuously infective members of its own species may have been, in the one case, eliminated from the population with which it is in contact.

SUMMARY.

Susceptible mice have been placed in contact with infective individuals of the same species, separated from them after a definite period, and placed in contact with a further group of normal mice. This process has then been repeated again and again, the number of groups exposed varying, in different experiments, from three to twelve. In this way the spread of infection has been limited to that occurring between any one group and the group immediately following it.

Under these circumstances infection has spread far less readily than was the case in other experiments, in which the mice were retained as a single population, and in which infection could spread in any direction among all the individuals at risk.

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