# THE EFFECT OF WITHDRAWING MICE FROM AN INFECTED HERD AT VARYING INTERVALS

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(With 1 Figure in the Text)

## Introduction

In a recent report (Greenwood *et al.* 1936) we included a short discussion of the few scattered observations that we had made on the effects of the dispersal of an infected herd (pp. 189–92). Briefly, we had found that the division of a herd, in which an epidemic due to *Bact. typhi-murium* was under way, into small isolated groups was followed by a greatly decreased rate of mortality in those groups when the dispersal was carried out at the beginning of the epidemic period. Reaggregation of the groups resulted in a fresh spread of the disease, but the final mortality was lower than in a similar herd which had not been dispersed during the earlier stages of cage life (Topley, 1922). In a subsequent experiment (Topley & Wilson, 1925) dispersal was carried out at a later stage of epidemic spread, and very different results were obtained. For the first three weeks or so after division into small groups there was no material difference between the mortality experienced by the dispersed and not-dispersed mice. But at about the 25th day the death-rate in each of the dispersed herds showed a definite decline, while that in the undispersed herds continued unabated for some further length of time.

These few observations were clearly in conformity with the reasonable view that the conditions of contact may exert an exceedingly important effect on epidemic spread, but that to secure much benefit from dispersal it must be carried out shortly after exposure to risk in the epidemic environment.

In the same report we discussed at some length (e.g. pp. 94 *et seq.*) the general problem of the evolution of disease in a herd, and pointed out that a fundamental datum was knowledge of the time relation of the process of infection. Our most precise, but limited, data (Topley *et al.* 1924) showed that by the end of 25 days about four-fifths of animals exposed to risk in an infected herd in which mouse typhoid was spreading had given proof of infection.

Another question intimately related to this is the relative resistance to infection of mice which have survived exposure to the environment for varying lengths of time. All our previous experiments have shown quite clearly that the average resistance of surviving mice increases with increasing



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cage age, but this resistance has never reached a point at which the risk of dying from the prevailing infection has been reduced to zero. We have made one or two attempts to measure how far variations in severity of exposure, as measured by prevailing death-rate in the cage, may, in fact, continue to influence the power of survival of mice which have successfully endured a relatively long period of cage life. Our first observations (Greenwood *et al.* 1930) suggested that mice of advanced cage age were substantially less susceptible to changes in the prevailing death-rate than mice which were relatively newcomers. Further observations (Greenwood *et al.* 1931) did not confirm this. A more detailed study was, therefore, made of our accumulated material (Hill, 1933) and led to the conclusion that variations of severity of exposure affected the mortality rate of mice of all observed cage ages. Previous survival in the cage, even of considerable length, did not render them indifferent to changes in that environment.

For instance, in a herd infected with *Bact. typhi-murium* there were 202 mice which entered the cage when for the 5 days previous to their entry the average daily death-rate had been very low, between 0 and 1%. The average length of life (limited to 60 days) of these mice after entry was 39 days. Contrasted with these were 340 mice which entered the cage when the daily death-rate for the previous 5 days had been relatively high, between 3 and 4%. Their mean length of life was only 24 days. Corresponding to these new entries were thirty-four mice which had survived 30 days in the cage, and for the last 5 days of that period were exposed to the low death-rate of 0–1%. There were also fifty-six which for the last 5 days of the 30 days they had lived in herd were exposed to the high death-rate of 3–4%. The average survival times of these two groups from cage age 30 were 38 and 22 days. Thus 30 days of cage life did not render the mice insensitive to variations in the mortality rate. Experiments with *Pasteurella* gave a similar result; but with the virus disease Ectromelia mice of older cage ages became, on the average, relatively indifferent to exposure to higher death-rates.

With the bacterial infections it was concluded that, though at each level of mortality in the herd mice of high cage ages survive in general longer than new entrants, yet the relative effect of variations in environment does not disappear with cage age. This conclusion, it will be noted, is based solely upon the behaviour of mice which continue to live *in the cage* after a certain exposure, and this method of analysis suffers from the disadvantage that the herd mortalities immediately before and after any given day tend to be highly correlated, so that mice that have just passed through a period of high mortality will be exposed to a higher *subsequent* risk than mice that have passed through a period of low mortality. A more satisfactory answer would clearly be reached by comparing the behaviour of mice of different cage ages removed to isolation after a certain exposure, and thereby debarred from any further risks, with that of mice of the same cage ages which continued to reside in the infected herd.

The objects of the present experiment were, mainly, to throw further light upon these three questions, viz. (1) the effect on individual mice of withdrawal from the herd at different stages of cage life, (2) the progress of infection at those different stages of cage life, and (3) the effects of long survival in the cage in relation to changes in the severity of that environment.

## THE EXPERIMENT

On 27 September 1934, twenty-five normal mice were each inoculated with 10,000 *Bact. typhi-murium* and herded with fifty normal mice. From 9 to 24 October three normal mice were added to the herd daily. On 25 October, and thereafter at weekly intervals, batches of sixty mice were added. Before entry to the cage each of these weekly batches was divided at random into two sets of thirty, every individual being distinguished by identification marks. The mice composing one of these sets were left in the cage indefinitely, until death or survival at the close of the experiment. Those composing the other set were removed to isolation in single cages after varying lengths of sojourn in the herd. They were kept in these separate cages until death or the expiry of a period of 60 days after isolation. The survivors at the 60th day were killed, bled and examined post-mortem, while the faeces of each isolated animal were examined once a week until death or the 60th day of isolation.

From 25 October 1934 to 27 June 1935 one-half of the survivors of each set of thirty mice originally selected to be isolated (or one over the half if the number were odd) was removed to single cages at the end of 7 days in herd. The other half was left in the herd until cage age 14 days when one-half of the survivors at this point of time was isolated. The other half was again left in the herd until cage age 21 days, when one-half of their survivors was isolated; and so on. This procedure led to a rapid accumulation of isolated mice which had spent only 7 days in herd but insufficient numbers which had had longer experiences of herd life. From 27 June to 17 October 1935, therefore, no mice were removed until they had spent at least 14 days in herd, when half the survivors were isolated and the remainder removed after longer periods in the same ratios as before. By these means the number of mice which had spent 14 days in herd was considerably increased, but mice of higher cage ages were still too few to give significant figures. From 17 October 1935 to 30 March 1936, therefore, no mice were removed until they had spent at least 21 days in herd, and from 30 April to 28 May unless they had spent at least 28 days in herd. By these means the numbers with different cage ages before isolation were made fairly substantial.

On 4 June the experiment was stopped owing to the occurrence of a death due to an infection with *Bact. enteritidis* (Gaertner).

### *Events within the herd*

The secular course of mortality in this herd was in no way remarkable. It rose rapidly to a high point, with a daily death-rate of some 5% at about

the 10th day, then fell with the fluctuations usual in a newly formed herd to a rate of 1·5–2·0% per diem between the last week of October and the first week of November 1934. A slow rise in mortality then set in reaching a peak of 3·6% towards the end of November. A rapid fall ensued and the mortality lay between the 1·5 and 2·0% levels until 9 February 1935, when a further decline took place and the prevailing figure was not much above 1%. At the beginning of March 1935 the death-rate began to rise and reached a maximum of 3·4% on 12 March. Some decline subsequently took place, but a second maximum of 2·6% was recorded on 8 April. For some months thereafter mortality was on a lower level, about the 1·5% point, but in both July and August epidemic waves were clearly visible, a peak of 3·8% being recorded on 6 August. The death-rate again declined but a rise ensued on 2 October, reaching the 3·5% elevation on 24 October. Thereafter the rate remained somewhat low but rose again in January 1936 and still further in February, remaining high for some weeks and reaching 3% at the beginning of March. From that point it fell slowly, remained very low throughout April 1936, with some rise apparent as the experiment was brought to a close (at the end of May 1936).

These remarks are primarily based upon the course of the total mortality, but, with a slight reduction of scale, apply equally well to the specific death-rate which ran a course almost parallel to that of the general rate.

Cage-age mortality in this herd, on the other hand, followed a materially different course from that usual in our experience. Our previous experience with mouse typhoid has been gained from herds to which daily additions of at most six mice were made. In these herds the invariable course of age mortality has been for the rate to increase to a maximum between the 25th and 30th day of cage life (see Greenwood *et al.* 1936, Table VII, p. 36 and Fig. 6, p. 38) and then to decline to a level considerably above that of the rate of mortality of uninfected herds but much below the maximum of an infected herd. This level has been maintained, at later cage ages, with fluctuations the significance of which we have not had sufficient experience to assess.

In the present experiment (see Table I) the rate of mortality rose nearly to its maximum level relatively early in cage life—by the 14th to 15th day—but to a peak considerably below that in previous experiments. The declension from this peak was relatively slight during the first 70 days of exposure. Indeed, when the mean rate of mortality at all ages between 9 and 70 days was applied to the exposed to risk of different seniorities it was found that the deaths expected on this basis differed from the deaths actually observed by more than twice the standard error of the expectations at only four points (the 35th, 39th and 44th days of cage age were in excess and the 63rd day in defect). The tendency for the rate of mortality at the older ages within this period to fall to a level much below the maximum was clearly slight. Between the 70th and 100th days of cage age the $q_x$ values fell significantly, indicating that, in this experiment, the relative advantage gained by prolonged survival

in herd was considerably delayed. A comparison is given between the past and present experiences in Table II which shows the relatively small differences between the probabilities of dying at different cage ages up to the 70th day in the present instance.

Table I. *Life table based on mice not transferred to isolation*

| Cage age in days | No. exposed to risk | Specific deaths | Nil found deaths | Total deaths | Specific $q_x$ | Total $q_x$ |
|---|---|---|---|---|---|---|
| 0 | 2188 | 1 | 1 | 2 | 0·0005 | 0·0009 |
| 1 | 2186 | 2 | 2 | 4 | 0·0009 | 0·0018 |
| 2 | 2182 | 1 | 5 | 6 | 0·0005 | 0·0027 |
| 3 | 2176 | 2 | 4 | 6 | 0·0009 | 0·0028 |
| 4 | 2170 | 3 | 11 | 14 | 0·0014 | 0·0065 |
| 5 | 2156 | 7 | 6 | 13 | 0·0032 | 0·0060 |
| 6 | 2143 | 8 | 6 | 14 | 0·0037 | 0·0065 |
| 7 | 2129 | 19 | 5 | 24 | 0·0089 | 0·0113 |
| 8 | 2105 | 20 | 6 | 26 | 0·0095 | 0·0124 |
| 9 | 2079 | 39 | 2 | 41 | 0·0188 | 0·0197 |
| 10 | 2038 | 38 | 3 | 41 | 0·0186 | 0·0201 |
| 11 | 1997 | 43 | 3 | 46 | 0·0215 | 0·0230 |
| 12 | 1951 | 38 | 3 | 41 | 0·0195 | 0·0210 |
| 13 | 1910 | 54 | 2 | 56 | 0·0283 | 0·0293 |
| 14 | 1854 | 61 | 4 | 65 | 0·0329 | 0·0351 |
| 15 | 1789 | 59 | — | 59 | 0·0330 | 0·0330 |
| 16 | 1730 | 45 | 2 | 47 | 0·0260 | 0·0272 |
| 17 | 1683 | 47 | — | 47 | 0·0279 | 0·0279 |
| 18 | 1636 | 43 | 2 | 45 | 0·0263 | 0·0275 |
| 19 | 1591 | 34 | 1 | 35 | 0·0214 | 0·0220 |
| 20 | 1556 | 33 | — | 33 | 0·0212 | 0·0212 |
| 25 | 1377 | 39 | — | 39 | 0·0283 | 0·0283 |
| 30 | 1188 | 27 | 1 | 28 | 0·0227 | 0·0236 |
| 35 | 1024 | 50 | 2 | 52 | 0·0488 | 0·0508 |
| 40 | 846 | 27 | 2 | 29 | 0·0319 | 0·0343 |
| 45 | 717 | 23 | — | 23 | 0·0321 | 0·0321 |
| 50 | 618 | 11 | — | 11 | 0·0178 | 0·0178 |
| 55 | 547 | 13 | 3 | 16 | 0·0238 | 0·0293 |
| 60 | 477 | 14 | — | 14 | 0·0294 | 0·0294 |
| 65 | 431 | 10 | — | 10 | 0·0232 | 0·0232 |
| 70 | 384 | 15 | — | 15 | 0·0391 | 0·0391 |
| 75 | 351 | 5 | — | 5 | 0·0142 | 0·0142 |
| 80 | 319 | 2 | — | 2 | 0·0063 | 0·0063 |
| 85 | 298 | 2 | — | 2 | 0·0067 | 0·0067 |
| 90 | 278 | 6 | 2 | 8 | 0·0216 | 0·0288 |
| 95 | 253 | 1 | 1 | 2 | 0·0039 | 0·0079 |
| 100 | 238 | 1 | — | 1 | 0·0042 | 0·0042 |

Table II. *The probability of dying within the next* 5 *days in three herds infected with mouse typhoid*

| Cage age in days | A 6 Six daily additions (all deaths) | A 3 Three daily additions (specific deaths) | A (present experiment) Added in batches of 60 (all deaths) |
|---|---|---|---|
| 0 | 0·0230 | 0·0077 | 0·0146 |
| 5 | 0·0575 | 0·0302 | 0·0547 |
| 10 | 0·1079 | 0·0934 | 0·1222 |
| 15 | 0·1564 | 0·1642 | 0·1302 |
| 20 | 0·2496 | 0·3237 | 0·1150 |
| 25 | 0·3185 | 0·4061 | 0·1373 |
| 30 | 0·2638 | 0·3469 | 0·1380 |
| 40 | 0·1031 | 0·1836 | 0·1525 |
| 50 | 0·0527 | 0·1280 | 0·1149 |
| 60 | 0·0518 | 0·0973 | 0·0964 |
| 70 | 0·0467 | 0·0965 | 0·0859 |
| 80 | 0·0132 | 0·0357 | 0·0658 |
| 90 | 0·0619 | 0·0000 | 0·0899 |

It has been observed that the conditions of the present experiment in respect of immigration were novel. Instead of daily additions of small numbers, a large batch of mice, sixty, was added every 7th day. We have data from no similar experiment with mouse typhoid. One in which the infection was Pasteurellosis we reported in 1925 (Greenwood & Topley, 1925). In that instance to an original group of twenty mice, eighty were added twice at an interval of approximately 2 months, and then three batches of fifty at intervals of approximately 6, 6 and 3 weeks. The secular rate of mortality was low and the data too scanty to justify analysis of mortality by cage age.

The peculiarity of the method now in question is that at intervals of 7 days the ratio of very young mice (in cage age sense) to mice of older age is sharply increased. An inspection of the secular course of $q_x$ shows an apparent tendency for the rate of mortality to show a maximum at intervals of 7 days. In view of the small numbers involved and the result of an admittedly rough test of sampling errors we should not claim to have demonstrated the reality of this appearance, but we think it is suggestive. We have always urged that at the back of and fundamental to the rates of mortality at *all* ages in a herd is the balance of cage-age constitution of the herd; we have thought that there was a reciprocal relation of risks between newcomers and old inhabitants. Not only is there the obvious risk to the newcomers due to exposure to a highly infective population, but the risk to the old inhabitants themselves is enhanced by the introduction of unsalted immigrants. The course of events in this experiment provides support for this belief, and it is our intention to investigate the point further.

Apart from its interest in relation to the general problem of the effect of changing herd constitution on herd mortality, the difference in the behaviour of mice at different cage ages in this and in previous epidemics of mouse typhoid has an important bearing on the interpretation of the results of the present experiment. As will be seen from Table II, if the trend of mortality with increasing cage age had followed the course expected from our earlier experience, the mice removed to isolation on the 28th and 35th days would have survived in herd beyond the period at which mortality was at its highest, and would have attained, either by selection, or natural immunization, or both, some degree of increased resistance to the disease. In fact, the highest value for the probability of dying within the next 5 days was not attained in the present experiment until the 40th day; and, instead of the well-marked peak observed in earlier epidemics, there is a plateau of relatively high mortality extending from about the 10th to the 50th day, which never attains the peak level encountered in our earlier studies. Instead of isolating, at the various periods selected, mice whose mortality rates, *if they had remained in herd*, would have been very different, we were in fact, after the 10th day of cage age, isolating groups whose experience in herd would have been very much the same.

This kind of difficulty is inherent in much of our work. In altering our experimental conditions in the ways required to obtain an answer to a particular question, we always run the risk of changing the evolution of the epidemic itself.

*The determination of infection rates*

The method of the experiment enabled us to study, as has been already pointed out, the after-histories (for 60 days) of mice which had survived in herd precisely 7, 14, 21, 28 and 35 days and were then withdrawn and kept in isolation in separate cages. The numbers removed after each of these durations of herd life are shown in Table III and, it will be seen, are reasonably large. Before entering into detail concerning their subsequent fate we must notice a limitation imposed by the nature of the experiment.

Table III. *Number of mice removed to isolation in separate cages after specified times in herd, and the proportion infected in each group*

| Length of time spent in herd. Days | Number of mice withdrawn to separate cages | Percentage estimated infected |
|---|---|---|
| 7 | 515 | 34 |
| 14 | 420 | 56 |
| 21 | 408 | 65 |
| 28 | 167 | 69 |
| 35 | 71 | 79 |

An ideal experiment from the present point of view would be one in which herd conditions were constant, epidemiologically speaking, throughout the whole period of observation and in which it was possible to examine every member *in* herd at short intervals of time. Under those conditions we should, within the limits of experimental and random error, have completely comparable series of animals exposed to risk of infection of 7, 14, etc., days, and each 7-day batch would be homogeneous with any other 7-day batch.

In fact mortality varied, as usual, in herd with time so that mice removed after 7 days' exposure in one phase of the experiment had lived in herd under mortality conditions different from those experienced in another phase. It will also be remembered that the removal to isolation of mice of different cage ages was not carried out equally over the whole course of the experiment. Mice of relatively low cage ages came predominantly from the earlier months, mice of relatively high cage ages from the later months of the experiment. Without such a limitation we could not have secured a large enough number of mice removed to isolation after prolonged survival in the cage. That it is a limitation is shown by the fact (see Table VIII) that the limited expectation of life in solitary confinement was correlated with the rate of mortality in the herd over the days immediately prior to isolation.

Another point to which we must refer before passing to the results of the experiment is the fact that our methods of determining the presence or absence

of infection in the mice removed to isolation were necessarily incomplete. The criteria of infection used were as follows:

(1) The isolation of *Bact. typhi-murium* from the faeces of each mouse at any time during its life in the single cage (weekly examinations).

(2) Specific agglutinins in the blood of mice killed after 60 days in single cages.

(3) Isolation of the organism from the tissues at autopsy of mice dying in herd or in single cages, or when killed at the end of 60 days' survival in the latter.

There is little doubt that the majority of the infected mice would be detected by criteria (2) or (3), especially by the latter; but a weekly examination of faeces (criterion (1)) would be insufficient to detect all those mice that, though suffering, or convalescent, from an infection on the day of isolation, became free from infection within the 60 days' period of observation. In the earlier experiment referred to above (Topley *et al.* 1924) faeces were examined from each mouse at risk on 6 days in each week. The scale of the present experiment, however, made such a procedure impossible, and we had to be content with less complete data in regard to this particular point. It follows that the infection rate at any cage age will be somewhat underestimated. Judging from our previous experience (see Greenwood *et al.* 1936, p. 58), we think that error under this head would not exceed 20% of the recorded infection rate, and would probably be considerably less.

The present experiment was, however, subject to an additional source of error which may have been more serious, and which was not constant over the whole experimental period. A certain number of mice, on necropsy, gave a growth of *Ps. pyocyanea* from their spleens; and though this organism does not seem to cause a fatal infection in mice under natural conditions it readily overgrows *Bact. typhi-murium* in culture, and thus leads to the latter organism being missed. Thus, of mice with a previous exposure in herd of 7 days 515 were transferred to single cages. Of these 148 were proved to be infected either by positive faecal culture, by spleen culture at autopsy, or by the demonstration of agglutinins, while 300 reacted negatively to all these tests. There were, in addition, sixty-seven mice which failed to excrete *Bact. typhi-murium* in their faeces, and which, when examined post-mortem, yielded culture of *Ps. pyocyanea* from their spleens. These mice could not, with certainty, be allotted either to the "infected" or "non-infected" category.

In calculating the percentage infected we have excluded these sixty-seven mice, or, in other words, we have presumed that the probability of their being infected was the same as in the 448 mice in which the determination of infection was not complicated in this way (this may rather overstate the infection rate, for none of the sixty-seven had been detected excreting the organism in the faeces before dying or being killed at the end of the 60 days). We have adopted this procedure for each group of mice removed from the herd after different durations of herd life.

We estimated by this means the proportion infected in each group surviving a given time in herd and removed to single cages. But to calculate the total proportion infected after $x$ days in herd, we must add, to those found to be infected after withdrawal, the number that died of the infection before reaching the cage age at which they would have been withdrawn to isolation. To reach the latter number we estimated the number of animals at risk from entrance to herd by using a life table for the herd (based on specific mortality), e.g. if at the end of 7 days there were $n$ survivors removed to single cages, this number was multiplied by $l_0/l_7$. An example will make the procedure plain. Of mice with a previous exposure in herd of 7 days 515 lived to be transferred to isolation. Of these, as previously stated, the condition of sixty-seven could not be determined owing to the growth of *Ps. pyocyanea*. Of the remaining 448 infection was proved in 148. The specific life table shows that on day 7 there were 9889 survivors out of 10,000 at day 0. We, therefore, multiply 448 by 10,000/9889 and reach 453 (in other words the 448 survivors at cage age 7 are 98·89% of the original entrants). The difference of 5 represents deaths from *Bact. typhi-murium* infection in herd, and so the total number of infections after 7 days in herd was $5+148=153$, and the proportion infected $153/453=33{\cdot}8$.

By this means we reach the infection rates given in Table III, namely 34% after 7 days' residence in herd, 56% after 14 days, and 65, 69 and 79% after 21, 28 and 35 days respectively. According to our criteria one mouse in five is still uninfected after 5 weeks in the herd environment. (With this method the results for batches removed to single cages at different times are aggregated before making the calculation. As the range of survivorship was wide from batch to batch the calculation was also made for each separate batch and an unweighted average of the results obtained. Very little difference ensued.)

If the present infection rates are compared with those previously found (Topley *et al.* 1924; Greenwood *et al.* 1936), it will be seen that in the present experiment the rate of increase of the proportion infected as time passed is less than in the earlier series. In the latter, 83% of entrants were infected or dead within 25 days, while here a proportion of 79% is reached only after 35 days. The discrepancies are in the same direction in the earlier days. We have little doubt that the explanation is that the count of infection in the previous experiment was more nearly exhaustive, for the reasons we have set out above. With these various limitations in mind we now pass to a consideration of our results.

*The effects of withdrawal to isolation*

In Table IV and Fig. 1 a comparison is made between the mortality experienced by the mice in isolation after various lengths of life in herd, and by those mice that had had the same preliminary experience of herd life but continued to be exposed in the cage. It will be seen that isolation had a

Table IV. *Probability of dying in the next* 5 *days* (*all causes of death*)

| Cage age in days (subsequent to previous duration of exposure in herd) | 7 days' previous exposure in cage A | | | | 14 days' previous exposure in cage A | | | | 21 days' previous exposure in cage A | | | | 28 days' previous exposure in cage A | | | | 35 days' previous exposure in cage A | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Single cages | | Cage A | | Single cages | | Cage A | | Single cages | | Cage A | | Single cages | | Cage A | | Single cages | | Cage A | |
| | $N$ | ${}_5q_x$ | $N$ | ${}_5q_x$ | $N$ | ${}_5q_x$ | $N$ | ${}_5q_x$ | $N$ | ${}_5q_x$ | $N$ | ${}_5q_x$ | $N$ | ${}_5q_x$ | $N$ | ${}_5q_x$ | $N$ | ${}_5q_x$ | $N$ | ${}_5q_x$ |
| 0 | 515 | 0·0971 | 1020 | 0·0755 | 420 | 0·1500 | 1288 | 0·1467 | 408 | 0·1569 | 1523 | 0·1215 | 167 | 0·2216 | 1255 | 0·1434 | 71 | 0·2394 | 1004 | 0·1753 |
| 1 | 515 | 0·1184 | 1009 | 0·0783 | 411 | 0·1509 | 1246 | 0·1380 | 400 | 0·1725 | 1490 | 0·1221 | 159 | 0·1950 | 1210 | 0·1364 | 68 | 0·2353 | 952 | 0·1597 |
| 2 | 507 | 0·1144 | 999 | 0·0971 | 398 | 0·1633 | 1205 | 0·1261 | 391 | 0·1841 | 1447 | 0·1209 | 152 | 0·1908 | 1173 | 0·1390 | 64 | 0·2500 | 929 | 0·1701 |
| 3 | 493 | 0·1136 | 980 | 0·1051 | 378 | 0·1429 | 1167 | 0·1174 | 373 | 0·1850 | 1410 | 0·1298 | 144 | 0·1667 | 1145 | 0·1633 | 58 | 0·1897 | 897 | 0·1661 |
| 4 | 474 | 0·0970 | 961 | 0·1186 | 370 | 0·1514 | 1136 | 0·1215 | 354 | 0·1610 | 1377 | 0·1373 | 138 | 0·1449 | 1108 | 0·1561 | 55 | 0·1818 | 864 | 0·1539 |
| 5 | 465 | 0·1054 | 943 | 0·1230 | 357 | 0·1625 | 1099 | 0·1165 | 344 | 0·1599 | 1338 | 0·1330 | 130 | 0·1000 | 1075 | 0·1600 | 54 | 0·1852 | 828 | 0·1534 |
| 6 | 454 | 0·1057 | 930 | 0·1280 | 349 | 0·1691 | 1074 | 0·1183 | 331 | 0·1601 | 1308 | 0·1414 | 128 | 0·1172 | 1045 | 0·1675 | 52 | 0·1731 | 800 | 0·1525 |
| 7 | 449 | 0·1158 | 902 | 0·1253 | 333 | 0·1562 | 1053 | 0·1301 | 319 | 0·1473 | 1272 | 0·1509 | 123 | 0·1220 | 1010 | 0·1743 | 48 | 0·1458 | 771 | 0·1517 |
| 8 | 437 | 0·1030 | 877 | 0·1117 | 324 | 0·1543 | 1030 | 0·1330 | 304 | 0·1184 | 1227 | 0·1369 | 120 | 0·1000 | 958 | 0·1597 | 47 | 0·1489 | 748 | 0·1524 |
| 9 | 428 | 0·0935 | 847 | 0·0956 | 314 | 0·1401 | 998 | 0·1283 | 297 | 0·1111 | 1188 | 0·1380 | 118 | 0·0932 | 935 | 0·1711 | 45 | 0·1333 | 731 | 0·1546 |
| 10 | 416 | 0·0865 | 827 | 0·0883 | 299 | 0·1070 | 971 | 0·1359 | 289 | 0·1038 | 1160 | 0·1621 | 117 | 0·0855 | 903 | 0·1672 | 44 | 0·1364 | 701 | 0·1398 |
| 11 | 406 | 0·0714 | 811 | 0·0986 | 290 | 0·0793 | 947 | 0·1383 | 278 | 0·0791 | 1123 | 0·1549 | 113 | 0·0531 | 870 | 0·1552 | 43 | 0·1163 | 678 | 0·1268 |
| 12 | 397 | 0·0554 | 789 | 0·0963 | 281 | 0·0641 | 916 | 0·1299 | 272 | 0·0772 | 1080 | 0·1509 | 108 | 0·0185 | 834 | 0·1547 | 41 | 0·0732 | 654 | 0·1239 |
| 13 | 392 | 0·0434 | 779 | 0·1001 | 274 | 0·0401 | 893 | 0·1355 | 268 | 0·0709 | 1059 | 0·1662 | 108 | 0·0370 | 805 | 0·1528 | 40 | 0·0500 | 634 | 0·1199 |
| 14 | 388 | 0·0412 | 766 | 0·1110 | 270 | 0·0370 | 870 | 0·1379 | 264 | 0·0606 | 1024 | 0·1738 | 107 | 0·0374 | 775 | 0·1510 | 39 | 0·0256 | 618 | 0·1133 |
| 15 | 380 | 0·0211 | 754 | 0·1114 | 267 | 0·0300 | 839 | 0·1275 | 259 | 0·0502 | 972 | 0·1595 | 107 | 0·0561 | 752 | 0·1516 | 38 | 0 | 603 | 0·1177 |
| 16 | 377 | 0·0212 | 731 | 0·1081 | 267 | 0·0375 | 816 | 0·1348 | 256 | 0·0391 | 949 | 0·1707 | 107 | 0·0748 | 735 | 0·1537 | 38 | 0 | 592 | 0·1267 |
| 17 | 375 | 0·0187 | 713 | 0·1094 | 263 | 0·0228 | 797 | 0·1619 | 251 | 0·0319 | 917 | 0·1668 | 106 | 0·0755 | 705 | 0·1390 | 38 | 0 | 573 | 0·1344 |
| 18 | 375 | 0·0267 | 701 | 0·1141 | 263 | 0·0342 | 772 | 0·1541 | 249 | 0·0241 | 883 | 0·1540 | 104 | 0·0577 | 682 | 0·1261 | 38 | 0 | 558 | 0·1308 |
| 19 | 372 | 0·0269 | 681 | 0·1057 | 260 | 0·0269 | 750 | 0·1587 | 248 | 0·0202 | 846 | 0·1525 | 103 | 0·0583 | 658 | 0·1231 | 38 | 0 | 548 | 0·1405 |
| 20 | 372 | 0·0296 | 670 | 0·1149 | 259 | 0·0270 | 732 | 0·1708 | 246 | 0·0203 | 817 | 0·1506 | 101 | 0·0495 | 638 | 0·1191 | 38 | 0 | 532 | 0·1278 |
| 21 | 369 | 0·0244 | 652 | 0·1135 | 257 | 0·0272 | 706 | 0·1785 | 246 | 0·0203 | 787 | 0·1499 | 99 | 0·0303 | 622 | 0·1125 | 38 | 0·0263 | 517 | 0·1296 |
| 22 | 368 | 0·0217 | 635 | 0·1087 | 257 | 0·0311 | 668 | 0·1571 | 243 | 0·0082 | 764 | 0·1505 | 98 | 0·0306 | 607 | 0·1170 | 38 | 0·0263 | 496 | 0·1190 |
| 23 | 365 | 0·0137 | 621 | 0·1176 | 254 | 0·0236 | 653 | 0·1669 | 243 | 0·0082 | 747 | 0·1526 | 98 | 0·0306 | 596 | 0·1258 | 38 | 0·0263 | 485 | 0·1134 |
| 24 | 362 | 0·0138 | 609 | 0·1478 | 253 | 0·0237 | 631 | 0·1632 | 243 | 0·0123 | 717 | 0·1381 | 97 | 0·0206 | 577 | 0·1334 | 38 | 0·0263 | 471 | 0·0955 |
| 25 | 361 | 0·0139 | 593 | 0·1400 | 252 | 0·0198 | 607 | 0·1516 | 241 | 0·0124 | 694 | 0·1254 | 96 | 0·0104 | 562 | 0·1299 | 38 | 0·0263 | 464 | 0·0970 |
| 26 | 360 | 0·0111 | 578 | 0·1419 | 250 | 0·0120 | 580 | 0·1448 | 241 | 0·0166 | 669 | 0·1211 | 96 | 0·0104 | 552 | 0·1395 | 37 | 0 | 450 | 0·0911 |
| 27 | 360 | 0·0111 | 566 | 0·1537 | 249 | 0·0120 | 563 | 0·1492 | 241 | 0·0166 | 649 | 0·1171 | 95 | 0 | 536 | 0·1269 | 37 | 0 | 437 | 0·0847 |
| 28 | 360 | 0·0167 | 548 | 0·1642 | 248 | 0·0121 | 544 | 0·1452 | 241 | 0·0207 | 633 | 0·1106 | 95 | 0 | 521 | 0·1286 | 37 | 0 | 430 | 0·0953 |
| 29 | 357 | 0·0084 | 519 | 0·1407 | 247 | 0·0081 | 528 | 0·1439 | 240 | 0·0208 | 618 | 0·1149 | 95 | 0 | 500 | 0·1180 | 37 | 0 | 426 | 0·1080 |
| 30 | 356 | 0·0056 | 510 | 0·1529 | 247 | 0·0081 | 515 | 0·1456 | 238 | 0·0126 | 607 | 0·1252 | 95 | 0 | 489 | 0·1125 | 37 | 0 | 419 | 0·1098 |

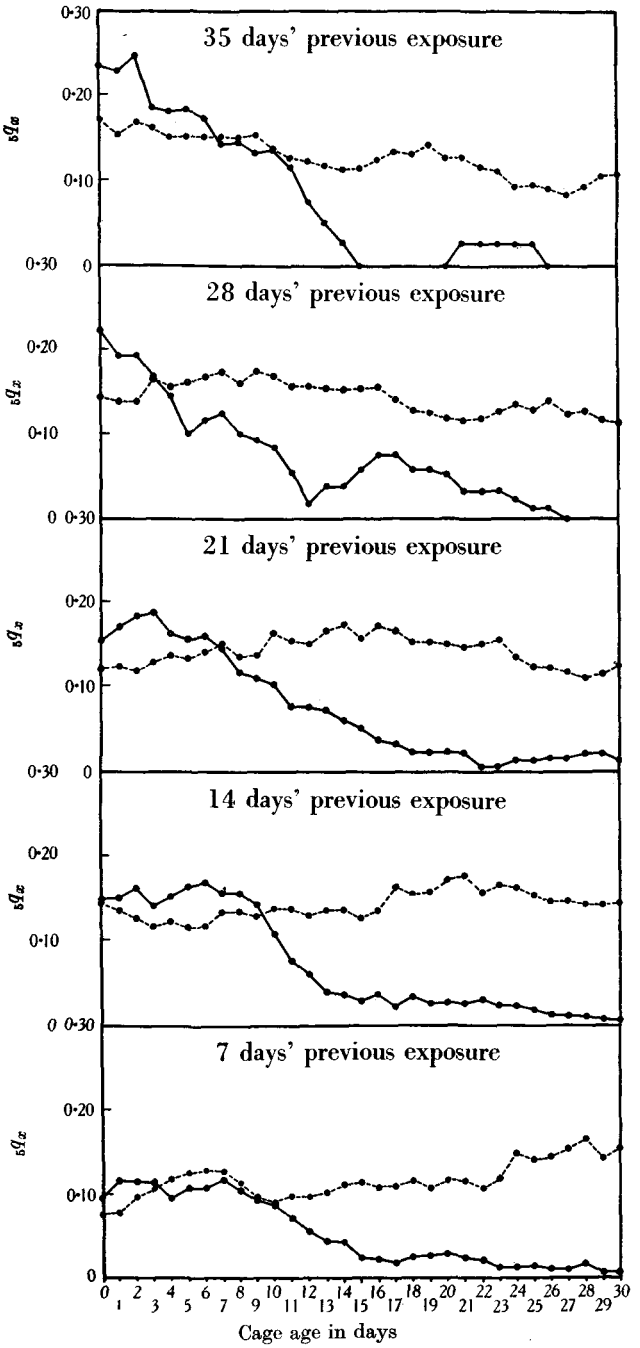


Fig. 1. Probability of dying in the next five days after exposure in herd for different durations of time.

—— In isolation - - - - In herd

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detrimental effect upon mortality during the first few days of life in separate cages. During these few days the mice in single cages died at a consistently higher rate than the mice which remained in herd. The abrupt change from their communal life had this unfavourable influence for some 4–7 days. On the other hand, their experience at later single-cage ages was very much more favourable than that of their colleagues left in the infected environment, and this advantage persisted however long they had previously lived in the herd. Selection by death and active immunization do not, within this time, produce immunity to the intense risks of herd life.

After 7 and 14 days' previous exposure in the herd, mortality in isolation changes little in the first 9 days, and the advantage of isolated mice does not become apparent until the 10th or 11th day. By that time many of the already mortally infected mice will have succumbed. The advantage of mice that survive this initial period increases rapidly to the 15th day and thereafter slowly. Mice with 28 and 35 days' previous exposure show the initial high death-rate already referred to, but it falls rather steeply soon after withdrawal. Having survived so long in herd they are, it seems probable, less likely to carry over a *mortal* infection and absence of further risks of infection has an immediate influence (though more than counterbalanced at first by the drawbacks of the change to single cages).

In Table V we have roughly summarized these detailed figures by computing the unweighted averages of the ${}_5q_x$ figures for each day in three 10-day periods, 0–9, 10–19 and 20–29 days after isolation, and similarly for non-transferred mice of the same previous exposure in herd. In the first 10 days after isolation there is no sensible difference between the mortality of the two groups with 7 days' previous exposure. Those with 28 days' previous exposure showed a slight advantage to the isolated, those with 14, 21 and 35 days' previous exposure some disadvantage. During this initial period the advantage of removal from the risks of herd life would seem to be offset by the factors, whatever they may be, which cause the change from communal life to isolation to react unfavourably upon mice already infected in herd. At later stages of isolation the advantage to the isolated mice is very consistent. At 10–19 days after isolation their mortality was about one-third of the rate of the corresponding mice in herd, at 20–29 days after isolation only about 12% irrespective of the previous duration of time they had spent in herd.

In Table VI we make another comparison of the isolated and not-isolated mice based upon the expectation of life and the percentage surviving during the entire period of observation (60 days). Taking this criterion there is a tendency for mice of considerable cage experience to fare somewhat worse in isolation, as compared with those remaining in herd, than mice of a shorter cage experience. Mice with 7 days of herd contact survived, in isolation, 41·6% of the possible days of life that they might have enjoyed, i.e. over and above that shown by the mice remaining in the cage. Two-thirds of them

Table V. *Summary comparison of isolated and not-isolated mice.* ${}_5q_x$ *values*

| Cage age in days (subsequent to previous exposure in herd) | Unweighted averages of ${}_5q_x$ values in 10-day periods: 7 days' previous exposure | | | 14 days' previous exposure | | | 21 days' previous exposure | | | 28 days' previous exposure | | | 35 days' previous exposure | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Single cages | Cage A | Single cages % of cage A | Single cages | Cage A | Single cages % of cage A | Single cages | Cage A | Single cages % of cage A | Single cages | Cage A | Single cages % of cage A | Single cages | Cage A | Single cages % of cage A |
| 0–9 | 0·1064 | 0·1058 | 100·6 | 0·1541 | 0·1276 | 120·8 | 0·1556 | 0·1332 | 116·8 | 0·1451 | 0·1571 | 92·4 | 0·1883 | 0·1590 | 118·4 |
| 10–19 | 0·0413 | 0·1043 | 39·6 | 0·0479 | 0·1415 | 33·9 | 0·0557 | 0·1611 | 34·6 | 0·0554 | 0·1474 | 37·6 | 0·0402 | 0·1274 | 31·6 |
| 20–29 | 0·0164 | 0·1343 | 12·2 | 0·0197 | 0·1571 | 12·5 | 0·0156 | 0·1331 | 11·7 | 0·0182 | 0·1251 | 14·5 | 0·0132 | 0·1061 | 12·4 |

Table VI. *Comparison of isolated and non-isolated mice. Expectation of life limited to* 60 *days and percentage surviving at* 60 *days*

| | No. of mice concerned | | Expectation of life limited to 60 days | | | | Percentage surviving 60 days | | |
|---|---|---|---|---|---|---|---|---|---|
| | In isolation | Remaining in herd | In isolation | In herd | Difference | Actual difference as % of possible difference* | In isolation | In herd | Ratio of percentages |
| After 7 days in herd | 515 | 1020 | 44·0 | 32·6 | +11·4 | 41·6 | 66·6 | 23·4 | 2·9 : 1 |
| „ 14 „ | 420 | 1288 | 38·3 | 28·3 | +10·0 | 31·5 | 56·2 | 19·8 | 2·8 : 1 |
| „ 21 „ | 408 | 1523 | 38·0 | 28·3 | + 9·7 | 30·6 | 56·6 | 20·7 | 2·7 : 1 |
| „ 28 „ | 167 | 1255 | 37·2 | 27·8 | + 9·4 | 29·2 | 55·1 | 22·8 | 2·4 : 1 |
| „ 35 „ | 71 | 1004 | 33·7 | 28·6 | + 5·1 | 16·2 | 49·3 | 25·1 | 2·0 : 1 |

* The maximum advantage to be conferred by isolation is taken to be the difference between 60 days and the average length of life of those mice remaining in the herd, e.g. mice who had spent 7 days in herd survived on the average 32·6 further days of life in herd. The additional advantage to the isolated mice might, therefore, be $60 - 32{\cdot}6 = 27{\cdot}4$ days. Actually they survived 11·4 more days than the non-isolated mice; 11·4 is 41·6% of 27·4.

survived the 60 days in isolation compared with rather less than a quarter of the mice with the same initial experience but remaining in the cage.

Mice with 14 days of herd contact survived only 31·5%, or 10% less than the previous group, of their possible days over and above their comparative group in the cage, and 56·2% of them survived the 60 days of isolation (again 10% less). With mice of longer exposures in herd there is a slight tendency for the absolute and relative advantages of isolation to decline (the number with 35 previous days in herd is, of course, small). This is to be expected. According to the figures set out in Table III, some 66% of the mice removed to isolation on the 7th day will have escaped infection in herd, and they will run no risk of contracting it in isolation. On the 14th day this figure will have fallen to 44%, and to 35, 31 and 21% respectively on the 21st, 28th and 35th days. Clearly, on this count alone, isolation after 35 days of herd life should be far less beneficial than isolation after a week. Actually our observations of the isolated mice, i.e. excluding previous deaths in herd for each batch, did not show quite such large differences between the degrees of infection. Of the mice removed after 7 days about two-thirds gave no signs of infection in isolation, whereas after 14, 21 and 28 days the figure was roughly one-half and showed little change with increasing duration of herd life; after 35 days it fell to 44% uninfected according to our tests. On these figures we should expect the older survivors to be in a less advantageous position than the younger (as observed) but not quite to the extent suggested by the figures of Table III.

If the relation between cage age and future expectation of life had been the same in this as in earlier experiments, there would have been an additional factor tending to decrease the benefit derived from isolation at late cage ages. The mice surviving to the 28th and 35th day would have been more resistant to the risks of reinfection in herd, an advantage that would not have affected their fate in isolation. In fact, however, as we have noted above, the course of events in the present epidemic was such that the mice remaining in herd had not reached the cage age at which this factor began to operate.

In Table VII we make a final comparison of the isolated and not-isolated mice. The expectation of life, limited in this instance to 30 days, is given for

Table VII. *Expectation of life limited to* 30 *days in* (1) *isolation*, (2) *in herd*

| Cage age in single cages | Previous length of exposure in the herd | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 7 days | | 14 days | | 21 days | | 28 days | | 35 days | |
| | (1) | (2) | (1) | (2) | (1) | (2) | (1) | (2) | (1) | (2) |
| 0 | 23·6 | *22·3* | 21·0 | *20·0* | 20·8 | *19·9* | 20·3 | *19·1* | 18·6 | *19·0* |
| 10 | 26·5 | *21·5* | 25·7 | *19·6* | 25·6 | *19·1* | 25·5 | *19·5* | 25·9 | *20·6* |
| 20 | 28·6 | *20·5* | 28·5 | *19·1* | 28·9 | *20·2* | 28·3 | *21·3* | 28·9 | *21·7* |
| 30 | 29·4 | *20·5* | 29·3 | *20·8* | 29·4 | *21·3* | 29·6 | *22·4* | 29·0 | *22·9* |

The italicized figures relate to the batches that entered the cage on the same day as the subsequently transferred mice but remained in the herd.

To make the expectations comparable their cage age has been commenced after 7, 14, 21, etc. days in the cage.

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different days after isolation, with comparable figures for those remaining in herd. On day of isolation (age 0) the transferred mice as a group have a negligibly longer expectation of life than the non-transferred mice, irrespective of the length of their previous sojourn in the cage. At any herd age the fact that many mice were not infected at the time of withdrawal is counterbalanced to some extent by the immediate, but transient, detrimental effects of isolation. On balance the expectation of life is, with one exception, slightly greater in the isolated mice than in those who remain in the herd. Though the differences are also relatively small, the longer the previous exposure in herd, within this limited period, the shorter the expectation of life on the day of isolation. After 10 and 20 days in isolation the status of the survivors of the mice in single cages improves. After 30 days their duration of life differs only fractionally from the maximum possible (30 days). There is no material difference between those whose experience of the herd was slight and those which were the relatively few survivors of longer periods of exposure.

Here again experience corresponds with expectation. The trivial difference in the expectation of life limited to 30 days, counting from the day of isolation, between the isolated mice and those remaining in herd is clearly due to the fact that, after any period of herd life between 7 and 35 days, a proportion of the surviving mice are already fatally infected, and will die whatever their environment may be. After 10 days in isolation, or in herd, many of these mice will have succumbed, so that the average behaviour of the groups under comparison beyond this period will depend to an increasing extent on mice whose fate is determined by what happens after day 0. With progressive increases in time to 20 and 30 days, the fatally infected mice will be still further eliminated by death, so that the isolated groups will be mainly composed of mice that have either escaped infection in herd, or have contracted an infection of a non-fatal type.

In a previous study (Hill, 1933) we concluded that variations in severity of exposure, as measured by prevailing death-rate in the cage, influenced the power of survival even of mice who had lived a relatively long time in the cage. The present experiment gives further support to this conclusion (*vide* Table VIII). With the small numbers of mice involved there is inevitably a good deal of fluctuation in the figures, but their general trend suggests that mice of some considerable herd experience were little, if any, less susceptible to changes in the herd environment (as measured by the prevailing mortality) than mice with shorter herd experience. With higher death-rates in the last 5 days of herd life the subsequent expectation of life in isolation and the percentage surviving 60 days of isolation tends to decline, and the percentage found to be infected in or at the end of that time tends to rise, whatever the seniority of the mice. Selection by death and natural immunization clearly do not lead to indifference to changes in the severity of the environment within the first 35 days of cage life; but, in this experiment, the period did not cover the onset of any demonstrable increase in resistance in herd.

Table VIII. *Effects of death rate in the cage upon subsequent experience in isolation*

| Death rate for 5 days in cage A before isolation | No. of days in cage A before isolation: 7 — No. of mice | 7 — $_{60}E_x$ | 14 — No. of mice | 14 — $_{60}E_x$ | 21 — No. of mice | 21 — $_{60}E_x$ | 28 — No. of mice | 28 — $_{60}E_x$ | 35 — No. of mice | 35 — $_{60}E_x$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 0·0100–0·0174 | 310 | 44·6 (100)* | 187 | 41·7 (100) | 185 | 40·0 (100) | 78 | 39·6 (100) | 36 | 32·6 (100) |
| 0·0175–0·0249 | 145 | 40·5 (91) | 159 | 37·4 (90) | 147 | 37·2 (93) | 63 | 35·2 (89) | 26 | 39·1 (120) |
| 0·0250 and upwards | 60 | 48·4 (109) | 74 | 31·6 (76) | 76 | 34·5 (86) | 26 | 34·7 (88) | 9 | 22·3 (69) |
| | Percentage surviving | Percentage infected | Percentage surviving | Percentage infected | Percentage surviving | Percentage infected | Percentage surviving | Percentage infected | Percentage surviving | Percentage infected |
| 0·0100–0·0174 | 68·7 (100) | 25·8 (100) | 64·2 (100) | 36·9 (100) | 60·5 (100) | 33·5 (100) | 60·3 (100) | 35·9 (100) | 44·4 (100) | 47·2 (100) |
| 0·0175–0·0249 | 58·6 (85) | 35·2 (137) | 52·8 (82) | 40·3 (109) | 54·4 (90) | 46·9 (140) | 50·8 (84) | 52·4 (146) | 61·5 (139) | 50·0 (106) |
| 0·0250 and upwards | 75·0 (109) | 28·3 (110) | 43·2 (67) | 47·3 (128) | 51·3 (85) | 48·7 (145) | 50·0 (83) | 38·5 (107) | 33·3 (75) | 55·6 (118) |

* Percentages of figures at 0·0100–0·0174.

The general effects of withdrawal to isolation appear, therefore, to be as follows:

Isolation has a detrimental effect upon the mortality experience for the first few days of life in single cages, but after those first few days the mice removed from the risks of herd life show a pronounced advantage over those remaining in the herd. If the subsequent history in isolation be considered for 30 days there is little difference between the relative advantages of mice which have spent only a short duration of time in the herd and those which have had considerable experience of herd life. If the period of observation be extended to 60 days the relative advantage is rather greater for mice which had been in the herd for only 7 days, in one-third of which infection was detected in isolation. There is a tendency for the advantage of isolation to decrease with increasing previous exposure in herd; but, with the exception of the sharp decrease in advantage of the mice isolated on the 35th day, which comprised a relatively small group, the differences are of doubtful significance. Early withdrawal will, of course, reduce the deaths that would subsequently have taken place in herd. If withdrawal be delayed it will nevertheless materially benefit the survivors at more advanced ages. Those survivors, as we have observed before, are by no means immune to their environment and the risks of reinfection.

Mice with considerable herd experience are still susceptible to changes in that environment, as measured by the death-rate prevailing in the cage. An upward swing in the death-rate will react unfavourably on mice of all seniorities.

These findings accord well with those obtained in earlier experiments on the effect of isolation or dispersal, so far as comparison is possible; but there is a fundamental difference in the methods employed, and in the questions at issue, which should, perhaps, be emphasized. The conclusion reached in our present investigation is that, *withdrawal from an infected herd, in which an epidemic infection is maintained at a high and relatively steady level by the influx of susceptible hosts, is advantageous at any period of exposure to risk, at least up to the 35th day*. This is clearly not analogous to a conclusion that the dispersal of a closed and infected herd into small groups, or as isolated individuals, will be of equal benefit over the same period. In the initial phases of such an epidemic, during its rise and peak, we should expect dispersal to have an advantage comparable to that observed in the present experiment; but as the epidemic waned, as it would if not maintained by the influx of fresh susceptibles, the risk in herd would fall, and the advantage of dispersal or withdrawal would decrease. It is probable that there would always be *some* advantage in either procedure; but it is very unlikely, either on *a priori* grounds or in the light of our earlier experiments, that the beneficial effect would maintain, during the later stages of a natural self-limited epidemic, the relatively high value observed under the very different conditions of the present experiment.

*The rate of infection*

We now pass to our further problem, viz. the accession of infected animals as length of exposure increases. As shown in Table III, 34% of the mice removed to isolation after 7 days in herd were infected according to our criteria (see p. 116). After 14 days in herd the proportion rose to 56%, after 21, 28 and 35 days to 65, 69 and 79%. These percentages are based upon reasonably large numbers of observations and it will be interesting to inquire whether they can be represented in any simple, orderly fashion. Of course, when the efficiency of any such method comes to be tested we must recur to the absolute numbers of observations, but for the moment we may consider the percentages as ultimate data. From the nature of the experiment, the starting figure of 100 is an absolute datum, at zero time no mice can be infected. Any "law" must at zero time reproduce the figure 100. We have then for the observed proportions not infected at the end of 0, 7, 14, 21, 28 and 35 days, the following series: 100, 66, 44, 35, 31, 21. The obvious experiment to make is to try to represent these figures by a geometrical progression. Performing the necessary calculations we find that the common ratio would be 0·7249. This leads to the series 72·5, 52·5, 38·1, 27·6 and 20·0. These are plainly very poor approximations to the observed values, a fact which becomes still more manifest if we compare the new infections at the realized rates in each 7-day period (in the 2019 mice of age 0) with those postulated by the "law". We have in fact:

| Observed | Calculated |
|---|---|
| 686 | 555 |
| 444 | 404 |
| 182 | 291 |
| 81 | 212 |
| 202 | 153 |

It is needless to compute the "goodness of fit"; the two series are quite incompatible. At first the rate of infection is much higher, then much lower, then again higher than the formula demands. That there should be such a discrepancy is by no means unexpected. If mice in herd could be likened to targets exposed to a steady bombardment of shots and an uninfected mouse to an unhit target, we should certainly expect the law of decrement of the number of uninfected mice to follow the rule of decreasing geometrical progression. But the *only* term in the comparison which seems to us reasonably appropriate is that of continuous bombardment; no doubt the risk of infection varies with secular time in any herd, but in view of the averaging process adopted by us, it is reasonable to think that, in this experience, the risk a mouse uninfected on the $n$th day of its sojourn runs of becoming infected on the $(n+1)$th day is independent of $n$, *so long as we give to infection the meaning of being hit* as in the simple schema. It is this proviso which fails. Infected mice in our classification are only a fraction of mice which have received a dose of infective material, viz. those mice who have reacted to the receipt of a dose by some demonstrable change in their biological rhythm. Expressing these

numerically in the usual way by a probability of becoming infected, we have 34% of the exposed to risk infected in the first 7 days, 33% of survivors infected in the next 7 days, and then successively 20, 11 and 32%. The risk is at a maximum at first, then declines to rise steeply in the last interval. These are the biological facts; we have to account for the decrement followed by a sharp increment.

Before arguing the case, it will be fitting to scrutinize some earlier data.

In one of our earliest joint papers (Greenwood & Topley, 1925), we discussed the question of the fluctuations of rates of mortality at later herd ages. The graphs suggested to us that after mortality had fallen to a quasi-constant level, low relatively to the maximal mortality but still high in comparison with the mortality of unexposed mice, there were depressions and elevations which might have some biological significance, expressing perhaps changes in the level of immunity. So far as cage ages beyond 100 days were concerned we could not then, and cannot now, satisfy ourselves that the oscillations, or fluctuations, were significant; the numbers at risk were too small. But when we are dealing with mortality at earlier herd ages, our data are more numerous. If the life tables published (Greenwood *et al.* 1930) with respect to *Bact. typhi-murium* infections, viz. $B_1$, $B_3$ and $B_6$ (specific deaths) are examined, there are concordant indications of maximal values of $q_x$ at *approximately* 15 days from entrance and thence at approximate intervals of 10 days. In $B_6$ $q_{14}$ and $q_{15}$ are much above $q_{13}$, and $q_{16}$ is less than either $q_{15}$ or $q_{17}$. Then $q_{26}$ is much greater than $q_{25}$ or $q_{27}$, $q_{37}$ exceeds $q_{36}$ and $q_{38}$, $q_{48}$ is larger than its predecessor and successor. In $B_3$ $q_{15}$ is an evident maximum, so is $q_{25}$, also $q_{34}$, $q_{42}$ and $q_{47}$. In $B_1$ $q_{15}$ is a maximum, $q_{25}$, $q_{34}$, $q_{39}$ also. We are not prepared to stress these facts. Quite apart from the mere sampling errors of the rates at higher ages, we find that the total numbers of maxima in the first 50 days of each experience do not appreciably differ from those to be expected in a random succession (see Kermack & McKendrick, 1937), but we are inclined to believe that there may be a real tendency to maxima at intervals of some 10 days in later herd experience and a quite unmistakable tendency to a first maximum near the 15th day of herd life.

We may now return to the main problem. What we have done is to follow out the life history of a group of mice from the moment of joining the herd, not indeed a specific group of individuals all entering at the same instant and living through the same secular conditions, but an average group which, on that account may be presumed to be exposed to *constant* risk. We must emphasize this point, because if we were concerned with a group of the same individuals then we should need to take account of the secular change in risk of infection. When a herd is started the initially infected animals are the only source of risk; as infection spreads to others this risk is multiplied, the rate of bombardment—to hark back to our old analogy—is not constant or, as Dudley would put it, the infection pressure varies. Our method of averaging has evened out this factor. We may suppose then that at the beginning of

exposure to the assumedly constant risk those animals which receive doses of infection will react in various ways; some will, apparently, ignore the reception altogether, others will acquire a fatal infection, others an infection which increases their resistance and so on. The number affected will be an unknown proportion of those receiving a dose; our method of analysis will catch either the mortally infected who die or those whose physiological processes are altered in some other way. It will not catch mere recipients of infective material whose general physiological reactions are unmodified. That after the first 7 days of exposure the rate of realized new infections decreases for several intervals might partly be explained by an elimination of the highly susceptible in the first period of exposure; but that cannot explain the subsequent increase of the number of new realized infections. Neither can it be wholly explained by a recovery from the infected state followed by reinfection. In so far as our technique is watertight, that obvious explanation is excluded, except in so far as effective infection might be produced and recovered from within a period of 7 days. If, for instance, on the 1st day of exposure a mouse became infected, in the sense that if at the end of 24 hours it had been removed to isolation it would, either by dying within 60 days or at the end of 60 days showing evidence of infection, have gone into the infected group; but if at the end of 7 days it had completely recovered, then if that mouse became reinfected between the 7th and the 14th day it would appear in our statistics as a new 7–14 infection. It is possible that we have here *a* factor of the subsequent increase, but we doubt whether it can be a large factor. A more probable explanation is this. Let us speak of the receipt by an animal of a dose of infective material as *contamination* to distinguish it from infection which implies a change in the quality of the recipient. It is, we think, difficult to believe that contamination can be other than fortuitous, so that the "law" of change with time of the numbers contaminated should follow the rule of geometrical progression. For if in any unit of time the chance of being contaminated is $p$, the succession of newly contaminated animals should be $p$, $(1-p)\,p$, $(1-p)^2\,p$, $(1-p)^3\,p$ and so on. In practice we should, of course, replace these expressions by those of Poisson's series, but the principle is the same. But there is no reason why the succession of new *infections* should follow this rule at all. It might be, for instance, that of the proportion $p$ contaminated in the first unit of time only a fraction, $kp$, say, where $k$ is less than unity, responded immediately by becoming infected, the remainder $(1-k)\,p$ might experience a latent period of several intervals and only figure in the infected class some weeks later. The result would be that the smooth declension in geometrical progression of the series of new infections would be distorted.

In principle the difficulty is similar to those discussed on pp. 96 *et seq.* of our Report to the Medical Research Council (1936), and our data are not sufficiently extended in time for any further arithmetical treatment to be useful. It is at least clearly established that infection, using that term as in

our Report "to denote any significant change in the host—death, illness or a change in specific immunity" (*op. cit.* p. 97), certainly does not follow a simple geometric law in time.

## CONCLUSIONS

The tentative conclusions which we should draw from this experiment are, therefore, as follows:

(1) If mice are added to an infected herd in large batches at regular short intervals, and a proportion of these are withdrawn at intervals of the same length, the life-table (cage age) mortality differs widely from that experienced in epidemics in which additions to the herd are made at a constant daily rate, and no mice are withdrawn. The difference lies in a rise to a lower peak of mortality during the earlier days of cage age, followed by a maintenance of the level of mortality then reached for at least 70 days, in contrast to the early rise to a higher level of mortality, followed by a rapid fall, which has been consistently observed when continuous additions are made.

(2) Withdrawal from an infected herd in which an epidemic is maintained at a high and steady level is advantageous at any period of exposure to risk, at least up to the 35th day. There is, as would be expected, evidence that the earlier the withdrawal, the greater is the benefit. The advantage of withdrawal is to a slight degree offset by the fact that the change in environment from herd life to isolation in a single cage increases the death rate in all groups during the first few days of life in isolation.

It should be noted that this conclusion applies only to epidemics in which the level of mortality is being maintained at a high rate by the steady influx of susceptibles. It does not follow that the dispersal into small groups, or into complete individual isolation, of animals exposed to a closed, and therefore self-limited, epidemic would have a like effect. Our previous experience suggests that the effect would in fact be slight once the epidemic had begun to decline.

(3) The results of this experiment confirm our earlier conclusions that mice remaining in an infected herd do not, through increase in resistance, become indifferent to fluctuations in herd mortality, during at least the first 35 days of herd life.

(4) These results also accord with our previous findings that the rate of infection in herd cannot be accounted for by any law based on a constant average risk of infection throughout herd life, if infection is defined as involving some detectable evidence of its presence. Since it seems clear that the average risk of receiving a dose of the infecting organism must be approximately constant when adequate numbers of mice are observed over an adequate period of time, there must be some factor, or factors, which render mice less susceptible to a change from the uninfected to the infected state as cage age advances. Our results in this, and in earlier experiments, suggest that there are fluctuations in susceptibility to infection during the later period of herd life.

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