THE SPREAD OF BACTERIAL INFECTION

SOME CHARACTERISTICS OF LONG-CONTINUED EPIDEMICS.

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(With 5 Charts.)

The experiments here reported form the preliminary steps in an attempt to investigate the laws which govern the spread of bacterial infection among an animal population, by observations carried out under conditions which are as far as possible experimentally controlled.

For many reasons the mouse has been selected as the most convenient host-species; and the preliminary work has been carried out with *B. Gaertner* as the infecting agent, since a considerable experience has already been gained of infections due to this organism.

In a series of investigations reported elsewhere (1), batches of mice were fed on cultures of *B. Gaertner*[1]. This organism was recovered from those individuals which subsequently died or fell sick, and the cultures so obtained were administered to other batches of mice. This process was repeated again and again, and it was found that certain of the strains isolated showed a greatly increased power of producing a fatal illness, when compared with the cultures earlier employed. After further passage carried out in the same way, this power decreased again, falling to its original level, or even lower.

Certain experiments were then carried out to determine whether the spread of infection by contact showed features which would indicate that such a variation in the character of the parasite is an important factor in the spread of the disease. For this purpose small epidemics[2] were started by placing normal mice in contact with others infected by feeding, and small numbers of mice were subsequently added at irregular intervals to test the risk of developing a fatal infection incurred by entrance to the cage at any given time. The results seemed to indicate that those normal mice added during

[1] This same organism was referred to in the earlier communication as *B. Danyzs*, but since the identity of the bacilli described under these two names seems to be well-established, and the name *B. Gaertner* has the claim of priority, it seems better to employ it.

[2] The word "epidemic" has been preferred to "epizootic" since it is probable that similar causes underlie such processes in whatever kind of living beings they occur, and it seems desirable to emphasise this similarity.

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the early stages of such small epidemics had little chance of survival, while of those which were added during the later stages a large part remained alive and apparently well, although at the time of their introduction to the cage deaths were still occurring.

These experiments were not carried beyond this stage. When a sufficient number of deaths had occurred to demonstrate the undoubted spread of infection from the mice originally fed to their healthy fellows, the addition of normal mice was in most cases stopped, and the sequence of events was then studied during the following 30 days or more.

The present investigation has been devoted to observing the effect of continuing the addition of normal mice to an infected cage over a long period of time, and of varying the mode of addition in certain ways.

GENERAL TECHNIQUE.

The technique adopted has differed little from that described in the communication referred to above. A certain number of mice have been fed on cultures of *B. Gaertner*. These animals have then been transferred to a suitable cage, and to this cage normal mice have been subsequently added. Each mouse added has been identified so that its subsequent fate could be determined. Each mouse found dead, or killed when dying, has been submitted to post-mortem examination; except in those cases in which the dead mice have been eaten by their companions, or have been too decomposed to render bacteriological examination possible. The more important naked-eye changes have been noted, and cultures have been obtained from the spleen, and from the heart. These have been examined by plating, and testing sub-cultures of selected colonies by agglutination against specific sera; and in many cases by complete fermentation tests. As a routine three colonies from each plate have been examined, when such plates yielded colonies of non-lactose-fermenting bacilli. In many cases more numerous colonies have been tested. It has been found to be of some advantage to submit the primary heart cultures to direct agglutination tests, and this has also been done in the more recent cases.

There are many points of technique not mentioned here, and they have been omitted, not because of their slight importance, but because a really satisfactory method has not yet been worked out. It seems better to reserve this subject for a separate communication, in which the difficulties to be overcome, and the possible ways of dealing with them, may be more fully considered. The experience gained during this investigation has made it clear that a somewhat elaborate technique must be developed and scrupulously adhered to if the spread of infection is to be kept under experimental control. It seems possible indeed that the risk of adventitious infection will always have to be faced, though disturbances caused in this way should not escape notice, and so lead to error.

The question of the health of the normal mice added is, however, so fundamental, that a brief statement must be made of the method adopted to limit

the possible errors due to this cause. Normal mice have been quarantined for at least seven days, usually longer, before introduction to the experimental cage. They have been kept in batches of 6 to 18, and if a death has occurred in any cage, no mouse has been added from that cage; unless all the other mice have remained well for several weeks afterwards, and a complete post-mortem examination of the dead mouse has failed to yield evidence of any known infection. When two or more deaths have occurred in any cage of normal mice the remaining animals in that cage have been destroyed. Among the particulars noted concerning each mouse added to the experimental cage has been the cage from which it came, and the date of transference. To each cage of normal mice is attached a card, stating the source from which the mice were obtained, the number originally in the cage, and the date on which they were brought into the animal house. On this card are recorded any deaths which occur and the post-mortem findings; also the date on which mice have been transferred to the experimental cage. In this way it has been possible to trace the history of any mouse from the time of its arrival, and in great measure to prevent the introduction of sick mice or their immediate contacts into the experimental cage. This procedure has probably sufficed to prevent infected mice being introduced as normal animals without the mistake being subsequently discovered. It has not sufficed to eliminate such adventitious infection. The main experiment under consideration was brought to a close by the appearance in the cage of another unrelated epidemic disease.

EXPERIMENT 1.

This experiment lasted from May 21st, 1919, until June 11th, 1920, on which date it was cut short by the appearance in the cage of the infection referred to. The epidemic started about the middle of October, 1919, and continued, in the manner to be described, until the conclusion of the experiment. The more important data are recorded in Chart I. The period, May 21st to September 17th, 1919, is omitted from the chart to economise space. During this time there was no indication of the active spread of infection. 47 mice were added to the cage, 14 of which had been fed on broth cultures of *B. Gaertner* (three separate strains), while 13 deaths occurred, mainly among the mice which had been infected by feeding. The sequence of events during this period is indicated in the table appended to this report. The chart is constructed as follows. On the upper base-line is indicated the number of mice added to the cage on each day. Each unshaded square corresponds to a single mouse. Immediately below this is a curve indicating the total number of mice in the cage. Beneath this again is a base-line on which are indicated the daily deaths, each shaded square corresponding to one mouse. The lowest curve indicates the average survival-time of the mice added to the cage on any given date. In constructing this curve, mice dying in less than three days after introduction to the cage have been disregarded; since, with one exception, no evidence of the infection in question has been found in the small number

of mice dying during the first two days of their sojourn in the cage. The majority of such deaths are apparently caused by fighting. In five cases, where one mouse has survived for a period out of all proportion to the survival-time of its fellows, it has also been disregarded on the ground that it probably possessed a peculiar and individual immunity.

The figures for the survival-times during the second half of May, 1920, and for the 11 days of June, must be regarded as approximate only. At that time a new infection arose in the cage and many of these mice died from this disease. The fresh epidemic arose, however, at a time when an outbreak was to be expected, and the survival-times are probably very nearly the same as those which would have been recorded had the original infection continued its course.

During the 388 days of the experiment, 782 mice were added to the cage and 728 deaths were recorded. On the last day included in this record 46 survivors were present in the cage. There is thus a deficit of eight mice unaccounted for in the chart. One of these was accidentally killed. The remaining seven were recorded as missing on varying dates. The explanation of this is readily found in the tendency of the living mice to eat their dead companions.

SUMMARY OF POST-MORTEM FINDINGS AND BACTERIOLOGICAL RESULTS.

It is proposed to publish later a short account of the pathology of this disease as it occurs in mice. It will suffice to point out here, that while very definite changes are often present, yet the bacteriological results form the only trustworthy criterion. In very many cases pure cultures of the organisms concerned may be obtained, while the only change observed post-mortem is a minimal enlargement of the spleen of no diagnostic significance.

Similarly the bacteriological results present many points of interest, which are being further investigated; but it seems better to postpone the discussion of them to another occasion and to include here only those facts which are necessary to demonstrate the nature of the infection studied.

The mice originally infected were fed on a 24 hours' broth culture of *B. Gaertner*. Two other batches of mice were infected by feeding them with cultures of this organism and were subsequently added to the cage during the pre-epidemic period. The strains employed for these latter feedings were isolated from mice which had themselves been fed on the original strain. All these strains were identical as regards their fermentation and serological reactions. Among the mice which died during the earlier stages of the epidemic many yielded pure cultures, not of *B. Gaertner*, but of an organism indistinguishable from it in its fermentation reactions, while failing to agglutinate with a high titre Gaertner serum. Subsequent examination of this organism has placed it in the "Suipestifer" group, using this term in its wide sense. It shows very close serological relationship to several strains of *B. suipestifer* (Mutton). As the epidemic progressed, strains of *B. Gaertner* or of this organism

were obtained from the great majority of dead mice examined. Some mice yielded pure cultures of *B. Gaertner*, others pure cultures of *B. suipestifer*. Very frequently both organisms were obtained from the same mouse. A study of the table appended to this report will show that it is impossible to separate the deaths due to one organism from those due to the other, even could we decide where to place those mice which were doubly infected. The question of the relationship of these organisms is being further studied, but for present purposes the epidemic must be considered as a homogeneous infection. The isolation of *B. suipestifer* from mice experimentally infected with *B. Gaertner* has been reported by many observers, and has been amply confirmed in the epidemic under consideration, in others to be referred to later, and in a series of control feeding experiments.

Briefly, 728 deaths were recorded during the course of the main experiment. Of these, 14 followed direct infection by feeding. Of the 714 mice which were infected by contact, 152 were not examined post-mortem, in most cases because they had been partially or completely eaten by their companions; from 228 mice, cultures of *B. Gaertner* alone were obtained; from 137, *B. suipestifer* alone was isolated; from 130, cultures of both organisms were obtained; while the remaining 67 mice gave negative bacteriological results. In those cases in which *B. Gaertner* or *B. suipestifer* were obtained, they were in almost all instances apparently unmixed with other organisms. The bacteriological results in the case of each mouse are indicated in the table at the end of this report.

General Results.

The whole experiment may be divided roughly into four periods. The first extends from May 21st, 1919, to September, 17th, 1919, and has been referred to already. From September 18th, 1919, and onwards, only normal mice were added to the cage. From this date until January 5th, 1920, the mice were added in such a way as to keep the total number in the cage roughly constant. Clearly, to add on each day exactly the number of mice found dead might lead to a chance arrangement, in time, of the earlier deaths becoming perpetuated in those occurring later, so that the form of the chart of mortality might come to be only a reflection of the method of addition of normal mice. While this was certainly not the case it is doubtful whether this disturbing factor was altogether avoided. From January 6th to April 27th, 1920, three normal mice were added each day, except on two occasions when none was added. The number of mice in the cage during this period varied from day to day, reaching a maximum immediately before each considerable wave of mortality, and falling to a minimum just before its cessation. During the final period from April 28th to June 11th, 1920, two normal mice were added daily instead of three. In considering the three stages of the actual epidemic it will be most convenient to deal with the last period first, and to join with it the last 25 days of the second epidemic period; for during this time the features

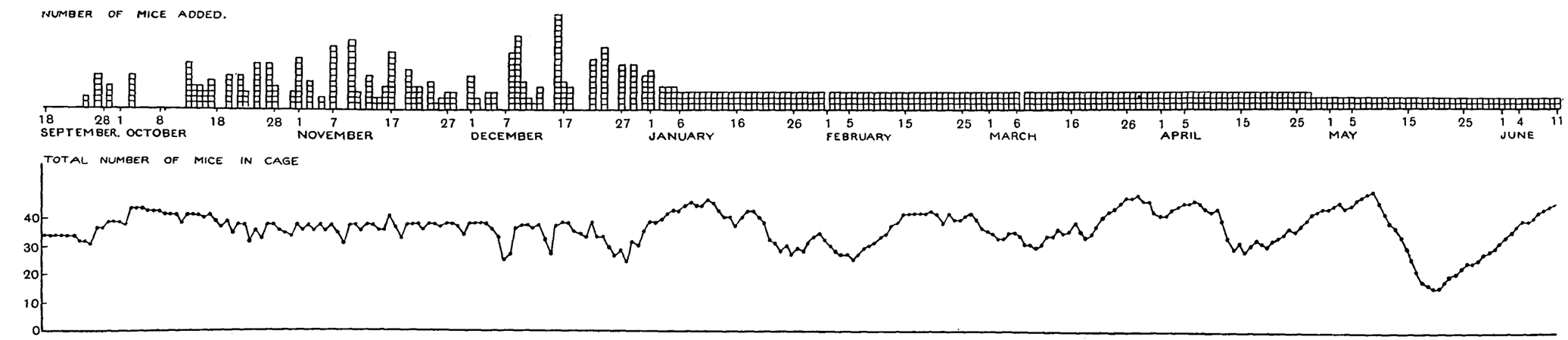

Chart I.

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which are of most interest, and which can also be traced in the preceding stages, are more strongly marked and hence more readily studied. The course of events during the period in question, April 3rd to June 3rd, 1920, inclusive, is recorded in Chart II, which is constructed on the same plan as Chart I with certain additions.

A study of this chart shows several striking facts. Although the normal mice were added regularly, the deaths neither occurred with the same

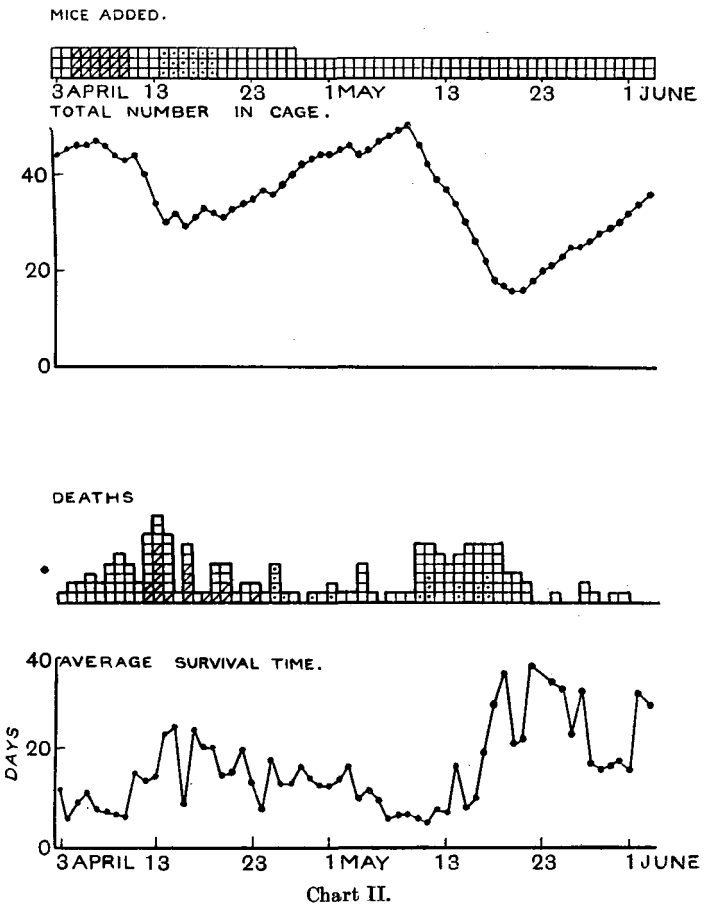

Chart II.

regularity, nor haphazard, but fell into two main groups, within which the daily deaths rose to a maximum and then fell again. Relatively few deaths took place in the intervening period.

If we now compare the distribution of deaths with the curve showing the total mouse population exposed to risk of infection, and with that showing the variation in the average survival-time of the mice added from day to day, certain features present themselves for consideration.

The curve, showing the total cage-population, falls during the latter part

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of the rise, and during the crest of the wave of mortality, reaching a minimum at a point slightly preceding the complete subsidence of the wave. It then rises again, reaching a maximum at a point just subsequent to the commencement of a new wave and again passes through the same phases. The curve showing the average survival-time shows corresponding fluctuations, but its maxima correspond to the minima of the cage-population curve, and *vice versa*. The average survival-time of normal mice introduced into the cage is at a minimum during the earlier stages of the rise of the wave, and at a maximum at a point subsequent to its crest but preceding its entire subsidence. Given the fact that the deaths, under such circumstances, occur in waves, it is clear that these results will follow in some measure; but it is worth while to follow a little more closely what actually occurs.

For this purpose two groups of mice have been selected which were added during the first of the two waves. The first group consists of 18 mice, which were added between April 5th and 10th inclusive, during the rise of the wave and when the average survival-time, as indicated by the lower curve, was at or near its minimum. These mice are distinguished among the squares showing the daily additions by marking them with a diagonal line. Their deaths are indicated in the mortality chart by marking the corresponding squares with a similar diagonal. The 18 mice, forming the second group, were added between April 14th and 19th, at a time when the wave was subsiding, and when the survival-time of the added mice was at or near its maximum. The addition and death of these mice are indicated in a similar way to that employed for the first group, a dot being substituted for the diagonal.

Tracing the deaths of these two groups of mice on the mortality chart, we find that all of those added during the rise of the wave died during its crest or subsidence. In this period only four deaths occurred among those mice which were added on later dates. Of the mice added during the second period, none died during this time, although the number of days which elapsed would have sufficed to allow for the death of a considerable proportion of them, judging from the average survival-time estimated for the whole period of the experiment. Seven of these 18 mice succumbed during the inter-epidemic period, but the remaining 11 did not die until the subsequent wave was well under way, and five of the 11 survived until the crest of this wave was passed. Before these 11 mice succumbed, 43 others, added at later dates, had met their death.

It will be well, at this point, carefully to consider the real nature of the facts with which we are dealing. It must be constantly remembered that we are concerned with a curve of mortality and not of morbidity. Were it possible to make an early diagnosis of this type of infection in living mice, our curve would clearly be displaced towards the left. It is hard to say what meaning should be attached to the figure expressing the average survival-time. It is not a measure of the infectivity of the cage-population; for concerning mild infections with a favourable termination our results yield no information.

Nor is it a measure of the risk of death; for this experiment tells us nothing of what the risk of death would be to the mice added at any moment, were the addition of normal mice immediately discontinued. It would seem to indicate, in some degree, the risk of contracting a severe and rapidly fatal infection; but the factors involved are too complex and too uncertain to allow of any descriptive term being employed, which would do other than confuse the points at issue. It seems better to record the survival-times as such, with the reminder that we know little of their meaning.

If now we turn to the earlier stages of the experiment we find the same general features displayed, but less strikingly, because the waves of mortality are no longer distributed in well-marked and relatively isolated groups, so that the end of one wave tends to overlap the commencement of the next. It is clear, however, that during the whole of the period over which the mice were added regularly to the cage, the deaths were neither distributed with the same regularity nor did they occur entirely without order; but showed, though less clearly, a distribution into groups, conforming with varying distinctness to the typical wave-form with its rise, crest and subsidence.

The same features are seen when we go further back to the period during which the normal mice were added in such a way as to keep the total number in the cage relatively constant. Here it is difficult to be certain that the distribution of deaths is not in some degree the reflection of the irregular method of introduction of susceptible mice. The well-marked maxima on December 16th and December 24th may have been largely due to this cause.

The fluctuations in the cage-population curve have already been considered for the period April to June, 1920, and the relation of their maxima and minima to the corresponding points on the mortality curve, and on the curve showing survival-time, has been referred to. If we now trace this curve backwards a very striking feature at once becomes apparent. As far back as the beginning of January, 1920, the same fluctuations are continued, and they show the same periodicity. Taking the whole period January to June there are four and a half such fluctuations. The curve shows five minima and four maxima, the fifth maximal point not being definitely indicated. The period of each complete fluctuation is about 40 days. During the period April to June the two fluctuations in the cage-population curve correspond to two definite waves in the mortality curve. In the period January to April the deaths are more evenly spaced, and do not form two well-marked groups; yet the same periodic fluctuation in the cage-population curve continues, and a closer study of the mortality curve indicates that the smaller groups of deaths, of which it is composed, fall into two large groups, whose maximal and minimal points bear the same relation to the corresponding points on the cage-population curve, as do the better marked maxima and minima of the last two waves of mortality. In the case of the period April to June, it has been seen that minimal cage-population corresponds with maximal survival-time of the normal mice added to the cage. In this respect again, the three curves show

the same relationship during the period January to April, when the curves of mortality and of survival-time are less distinctive. There is thus a strong suggestion that some regularly repeated cycle of events, with a periodicity of about 40 days, underlies the phenomena observed.

A difference in the general form of the cage-population curve may be noted according as the deaths occur in large isolated groups or are more evenly distributed in time. In the former case the epidemic wave causes a rapid decrease in the cage-population, which slowly rises again to its maximum during the period intervening between this wave and the next. The minimal point in such a case occurs not long after the maximum, and the descent towards it is steep, while the ascent to the next maximal point is relatively slow, and the distance, separating the minimum from the maximal point which follows it, is considerably greater than that separating it from the preceding maximum. When the deaths occur in smaller and more evenly distributed groups, the fluctuations in the cage-population curve are less wide, and the minimal points tend to lie approximately midway between the neighbouring maxima.

If we trace this curve still further back, we are unable to follow its fluctuations, since, during the period October, 1919, to January, 1920, the normal mice were added in such a way as to keep the cage-population relatively constant. A very instructive point may, however, be noted. If the process during this period was essentially the same as during the subsequent six months, it might be expected that more mice would have to be added on those dates which would correspond to the minimal points in the cage-population curve during the later stages. An examination of the upper line of the chart, showing the addition of normal mice, indicates that such was the case, though the manner in which mice were added excludes any accurate determination on this point.

The forced termination of this experiment did not allow of any conclusion being arrived at, as to the possible relationship between this periodic fluctuation of the total cage-population and the rate at which normal mice were added, though such seems highly probable. During the earlier stage, when mice were added in such a way as to keep the cage-population relatively constant, the average daily additions were 2·83. During the next period three mice were added daily, except on two days when none was added, the average daily additions for the 113 days being thus 2·95. During the last 45 days of the experiment the daily additions were decreased to two, but the experiment closed before one could expect the appearance of any variation in the periodicity which might have followed this change in the rate of addition. This point therefore has still to be examined.

FURTHER EXPERIMENTS.

If the results of this experiment, and of those previously reported, be considered together, it is difficult to avoid one very important conclusion. In the present study it has been shown that if normal mice are added from day to day to an infected population they will all eventually succumb, provided that further normal mice are added at a certain rate. The period of survival of any given batch of mice will vary according to the time at which they are introduced to the cage. If their entrance coincides with the early part of the rise of an epidemic wave, as judged by a mortality curve, their survival will be short. If they are introduced during the latter part of the decline of such a wave they will live, on the average, much longer, longer indeed than mice subsequently added to the cage.

In an earlier series of experiments it was found that normal mice, introduced among an infected population during this latter period, seemed in many cases to survive indefinitely, and without showing any observable departure from their normal condition. Should both these findings be confirmed it is clear that, among a population exposed to an epidemic infection, there will usually be a certain proportion who will, if the community concerned be living a relatively isolated existence, survive indefinitely. If, however, fresh susceptibles mingle with this surviving population in any considerable number the epidemic will break out afresh, and among the victims will be those individuals who have passed through the earlier epidemic wave.

There is, however, a very important difference between the earlier experiments and that dealt with in the present report. In the former the addition of normal mice was in all cases stopped after a comparatively small number of deaths had occurred, as the result of contact infection. In the present instance the process has been continued over a long period of time, and hence the virus has been given every opportunity of acquiring its maximal degree of infectivity and of virulence. The two series are therefore not strictly comparable. In order to study more fully the actual effect of the addition of normal mice on the survival of those previously introduced to the cage, two further epidemics were started, by feeding three normal mice in each case with a culture of *B. Gaertner*, and thereafter adding three normal mice daily to each of the two cages. When the mortality curve, combined with the bacteriological results, showed an epidemic of the desired type to be well under way, the additions were stopped and the subsequent course of events observed. In this way conditions were obtained strictly comparable to those existing in the main experiment during the time when three normal mice were added daily.

The course of events is shown in Charts III and IV. The additions, deaths and survival-times are indicated as in Charts I and II. The shaded squares, among those which show the added mice, correspond to animals which survived beyond the time-limits of the experiment. Similarly, the arrow above

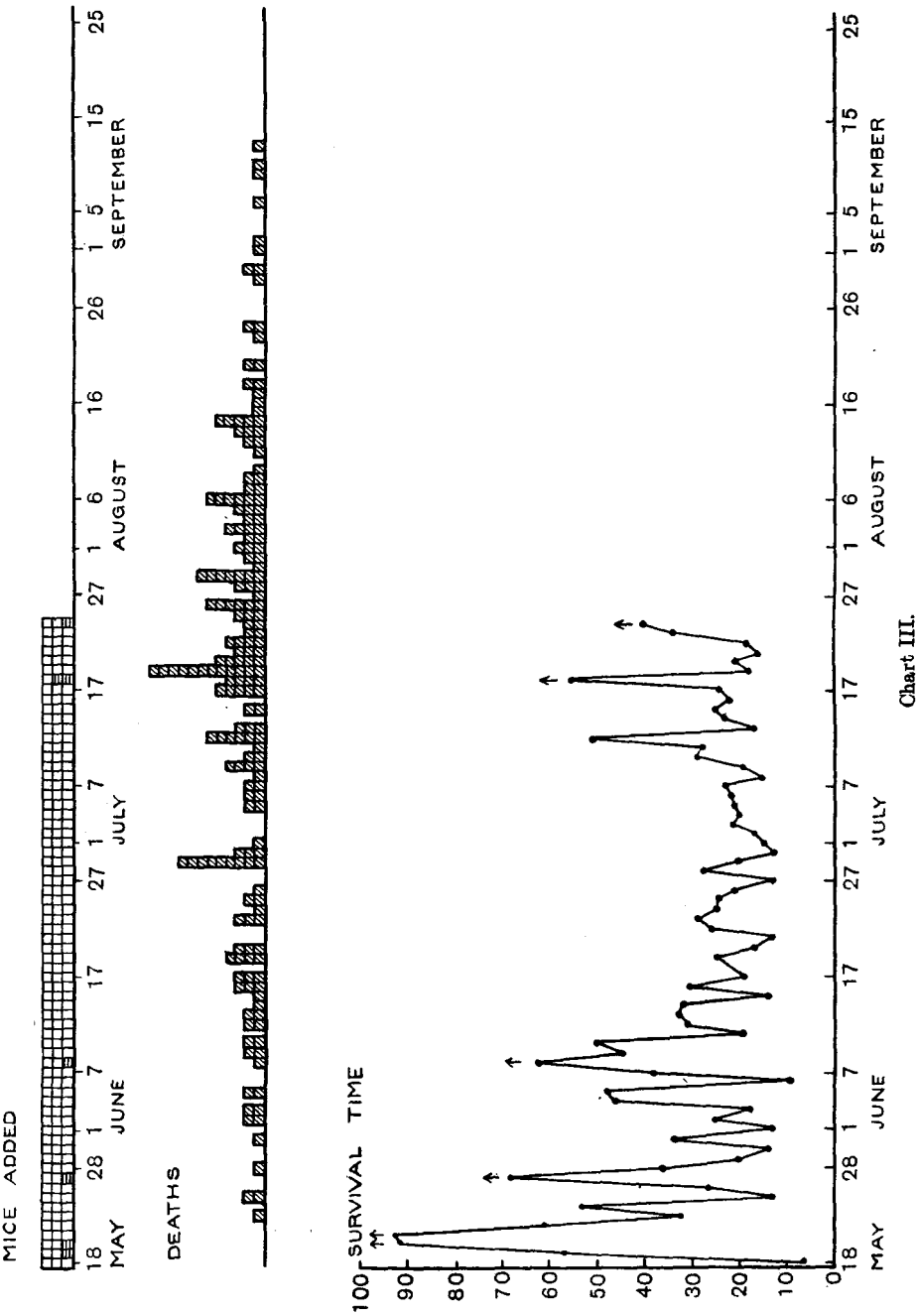

Chart III.

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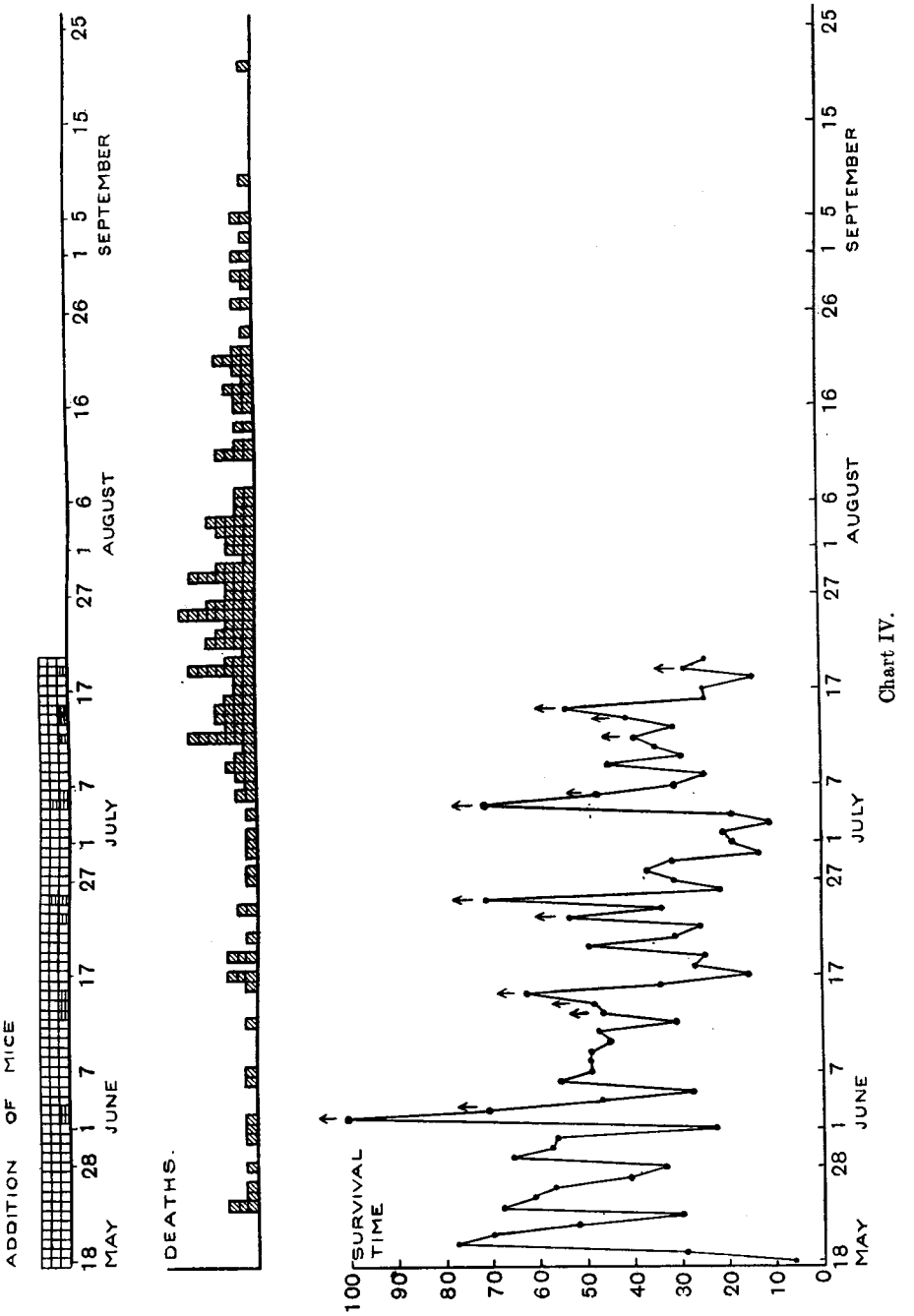

Chart IV.

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the corresponding points on the curve of survival-times indicates that the actual average value would have been higher had the experiment been continued longer. Certain points in connection with these charts will be referred to again, but the significant results as regards the effect of stopping the addition of normal mice are set out in Chart V.

In this chart, five dates have been selected during the period of the main experiment when three daily additions were made. They correspond to different phases of the epidemic, and together cover the whole of the period concerned. The deaths of those mice which were alive in the cage on the dates selected have been traced, and the percentage of these mice surviving on each subsequent day is indicated on the chart. Curves A to E have been plotted in this way. Curves F and G indicate, in exactly the same manner, the rate of death of the survivors in the two later experiments after the addition of normal mice had been stopped.

The results are quite definite. Taking the five curves A to E, the survivors had fallen to below 5 per cent. at points varying from the 15th to the 28th day. The actual number of survivors on these dates was two in the case of curve C, and one in each of the others. The fact that the curves do not reach the zero line is due to two mice which survived for a period out of all proportion to the life of their companions.

Taking the two curves, F and G, constructed from the experiments in which no further mice were added after the day on which these observations started, it will be seen that there is nothing distinctive in their course during the first ten days. From thence onward, however, the percentages of survivors in these two cages are markedly in excess of those in the cage to which normal mice were being added. Thus on the 15th day the average figure taken from curves F and G is 47 per cent., from curves A to E 13·4 per cent. On the 30th day, when curves A to E had been discontinued, and when there was in this cage only one survivor, representing less than 5 per cent. of the initial population, 38 per cent. of the mice were still alive in the experiment from which curve G was constructed, and 20 per cent. of those referred to by curve F. On the 60th day the percentages in these cages were 14·5 per cent. and 7 per cent. respectively, and deaths had practically ceased to occur.

It is clear, then, that an epidemic of this kind, which has been allowed to develop to its full tide, even if no further additions be made to the susceptible population, will lead eventually to the death of the great majority of the individuals exposed to risk, but a certain proportion will survive. It is equally clear that the rate of extinction of the surviving population will be very much greater if more susceptible individuals be introduced, and that under these circumstances complete extinction of the original survivors will ultimately result.

One other point must be noted in comparing these results with those obtained in earlier experiments in which the total population exposed to risk was very much smaller. In these cases the survivors under observation were

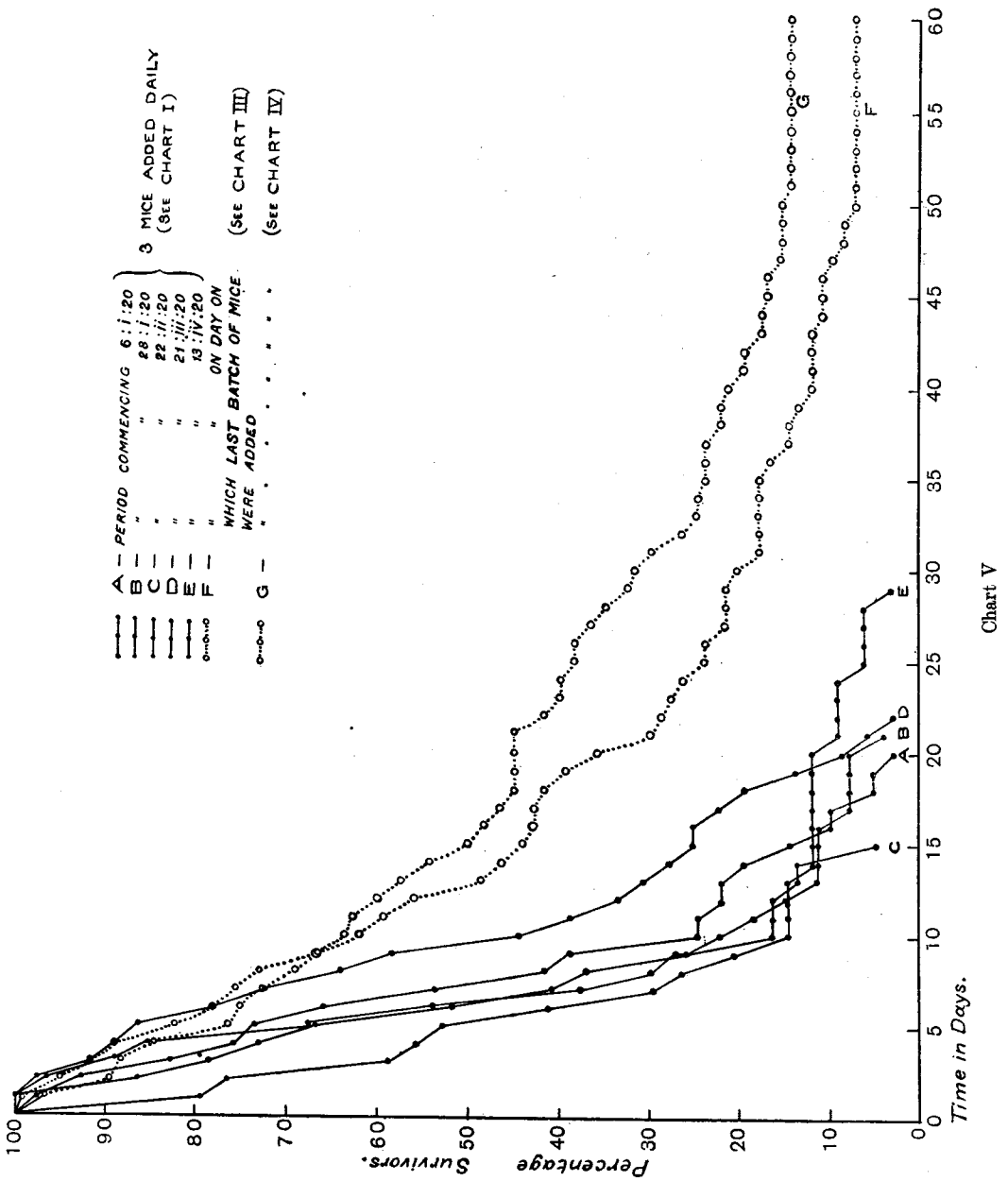

Chart V

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relatively very few. In the two experiments recorded in Charts III and IV, the surviving population, at the time when the addition of normal mice was stopped, numbered in one case 118 and in the other 84; so that there was ample opportunity for further passage of the parasite to and fro, from host to host. What the result would be of taking a population exposed to the same risk and segregating them in small groups is a problem that has still to be answered.

One other point in connection with these experiments deserves attention. An examination of Charts III and IV shows that, while the mortality curve as a whole rises and falls, yet this large group of deaths is clearly subdivided into smaller groups showing definite maximal points, and that this character is as well marked after the addition of normal mice has ceased as in the earlier stages. The maxima in Chart III occur with a suggestive regularity, and though Chart IV is less regular in this respect they both suggest that the deaths tend to occur in small groups, rising to a maximum and falling again in a period of some five to ten days. Successive groups vary in size in such a way as to form a mortality curve showing a fluctuation with a much longer period. The maximal points in the curve of survival-time, and the distribution among the added mice of those which ultimately survived, suggest as strongly that some fluctuating process with a relatively short period is concerned with the course of events, though here Chart IV is more striking than Chart III. It will be noted too that if the curve of survival-time is to be trusted this fluctuating process is in evidence in the pre-epidemic period. In Chart I, referring to the main experiment, it was noted that the mortality curve showed this same peculiarity, and that, while the cage-population curve showed a fluctuation with a period of some 40 days, the large groups of deaths, corresponding to the phases of this curve, were subdivided into smaller groups. Further reference to this chart shows that these smaller groups exhibit a striking resemblance in their general arrangement and in the interval between their maximal points to those observed in Charts III and IV.

If we try to account for the long survival of certain of the mice, and for the indefinite prolongation of life in some cases, it is hardly possible to believe that the latter have completely escaped infection, or that the former were only infected shortly before the fatal issue. It seems far more probable that these long-lived individuals owed their survival to the fact that, at the time they were added to the cage, the chances were in favour of their acquiring a relatively light infection, which increased their resistance to subsequent attacks of the parasite. It is difficult to account in any other way for the prolonged survival of certain of the mice added during the pre-epidemic period in the experiments recorded in Charts III and IV.

THE CONDITION OF THE SURVIVORS.

The actual condition of the individuals which remain as the survivors of a considerable epidemic is a point of obvious interest. The epidemic recorded in Chart IV was originally started by feeding three mice upon a culture of *B. Gaertner*, but, from the start, *B. suipestifer* was isolated from the great majority of the mice which died, while *B. Gaertner* was but rarely recovered. On the day when the last batch of normal mice was added to this cage its population numbered 118. 77 days later there were 15 survivors. All of these appeared in perfect health. These 15 mice were killed and examined post-mortem, cultures being obtained from the heart, spleen and liver in each case. The small portion of liver removed included the gall-bladder. The results are given in Table I, together with the more important details in the history of the mice concerned.

Table I.

Showing P.-M. Findings in Apparently Healthy Survivors from Experiment III (see Chart IV).

Batch number of mouse	Days in cage	Condition of spleen*	Results of cultures from†		
			Heart	Spleen	Liver
16	125	+	O	S	O
17	124	+	O	S	S‡
27	114	+	O	O	O
28	113	+	O	O	O
29	112	+ –	O	O	O
37	104	+	O	S	S
39	102	+	O	S	S
39	102	+ +	O	S	S
49	92	–	O	S	S
49	92	+ –	O	S	S
50	91	+ –	O	O	O
56	85	+ +	S	S+G	O
58	83	+ +	O	O	O
59	82	+	S	S	O
63	78	+ –	O	O	O

* – =no enlargement, + – =very slight enlargement, + =moderate enlargement, + + = great enlargement.

† S = *B. suipestifer*, G = *B. Gaertner*, O = Sterile or lactose-fermenting bacilli only. (In almost all cases the organisms were present in pure culture.)

‡ In this mouse there was a small chronic intraperitoneal abscess just below the anterior margin of the liver which gave a pure culture of *B. suipestifer*.

These results are somewhat surprising. From eight of the 15 mice cultures of *B. suipestifer* were obtained, and from one mouse both this organism and *B. Gaertner*. In the remaining six mice the bacteriological results were negative. In all the positive cases a culture of the organism concerned was obtained from the spleen. In two cases, the heart cultures were positive and the liver cultures negative. In six, the cultures from the liver gave positive results but not those from the heart. In one case *B. suipestifer* was obtained from the spleen alone.

Only four mice showed any marked abnormality post-mortem. In three of these there was marked splenic enlargement. In the other there was a small chronic intraperitoneal abscess, from the pus of which a pure culture of *B. suipestifer* was obtained. The remaining mice, with one exception, showed slight splenic enlargement, but of a degree which is common among mice dying from a variety of causes. With regard to the heart cultures, it should be mentioned that these were obtained by cutting away the apex of the heart and dropping it into a tube of broth. The two positive cultures obtained cannot therefore be regarded as definite evidence of the existence of bacteriaemia.

At this stage there is little point in speculating on the exact meaning of these results. Of 15 apparently healthy mice, 9 were harbouring in their tissues, and especially in the spleen and liver, the causative organism of the epidemic through which they had survived. Their sojourn in the cage had varied between 78 and 125 days. No deaths had occurred in the cage for 14 days and only two during the last month. It seems certain that some state of equilibrium had been arrived at, and that the mice which yielded the positive cultures were acting as carriers. What would have happened had a considerable number of susceptible mice been added at this point? It seems likely that a new spread of infection would have occurred; that a proportion of the newcomers would have died, while the old inhabitants of the cage remained unaffected; but that eventually these in their turn would have succumbed. This point is being more particularly examined in further experiments.

SUMMARY AND CONCLUSIONS.

The results so far obtained have raised many questions and answered few of them. The important rôle played in the spread of epidemic disease by the re-accumulation of a susceptible population is clearly indicated. It seems not unreasonable to hope that valuable information as to the effect produced by variations in the rate of such re-accumulation, and on other matters, may be obtained by the satisfying method of direct experiment. The bearing of such information on the well-known fluctuations in the incidence of epidemic diseases, and especially perhaps of those which fall most heavily on children, are too obvious to need emphasising.

The following conclusions seem permissible at the present stage:

(1) If susceptible mice be continuously added to an infected population the spread of infection will continue over a long period of time. There is no evidence that this period has a limit.

(2) When susceptible mice are added continuously and at a constant rate to an infected population, the spread of infection, as judged by a mortality curve, is propagated in regularly recurring waves. These waves are most easily observed by noting the fluctuations in the total cage-population. It seems probable that the period of these fluctuations will be found to depend

on the rate of addition of susceptible individuals, but this point has still to be determined.

(3) The actual deaths may occur in large groups, with intervals during which deaths are few and far between, or they may fall in a succession of smaller groups, increasing and diminishing in size to form the larger waves. In all cases there is this tendency for the occurrence of such small groups of deaths with definite maximal points. There would seem to be two fluctuating processes, the one superimposed upon the other.

(4) The average survival-time of mice added to the cage, and their chance of ultimate survival if no more susceptible mice are introduced, vary according to the phase at which they are added. If they gain entrance to the cage during the rise of a wave they are unlikely to live for long. If they are introduced during the fall of a wave their chances of survival are greatly increased, and they will usually outlive mice which are added at a later date but at a time before the commencement of the next wave.

(5) The rate of extinction of a population, among which infection is actively spreading, will be far less rapid if they are kept isolated, than if further susceptible individuals continuously gain access to them. A proportion of the infected population, which would have survived indefinitely under the former circumstances, will die under the latter.

(6) The ultimate survivors among such a population have not escaped infection, but have successfully resisted it. A considerable proportion of them are harbouring the causative parasite in their tissues.

My sincere thanks are due to my colleagues, Dr H. B. Weir and Dr G. S. Wilson, for their constant help, and to Mrs Phyllis Worthington whose assistance in this work I have been able to obtain by the aid of the Medical Research Council.

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APPENDIX.

Table showing addition and deaths of mice and bacteriological results of post-mortem examinations. (See Chart I.)

G = *B. Gaertner* isolated post-mortem.
S = *B. suipestifer* isolated post-mortem.
Nil = Examined post-mortem, but neither organism isolated.

Date	Mice added	Batch No.	Mice died	Batch No. of dead mice	Bacteriological results
1919					
May 21	6	1	—	—	—
„ 24	6	2	—	—	—
„ 28	6	3	—	—	—
„ 30	—	—	2	1	G
				3	Not examined
„ 31	6	4	1	1	G
June 16	—	—	1	4	Not examined
„ 17	—	—	1	1	G
„ 18	4	5	—	—	—
July 7	6	6	—	—	—
„ 21	—	—	3	6	Nil
				6	G
				6	G
Aug. 19	—	—	1	6	G
„ 26	—	—	1	5	S
„ 30	8	7	—	—	—
Sept. 3	—	—	2	7	S
				5	Nil
„ 15	—	—	1	7	Nil
„ 16	5	8	—	—	—
„ 24		—	2	8	Nil
				8	G
„ 25	2	9	2	1	G
				8	Nil
„ 26	—	—	1	8	Not examined
„ 27	6	10	—	—	—
„ 29	4	11	2	10	Nil
				8	Nil
Oct. 2	—	—	1	10	Nil
„ 3	6	12	—	—	—
„ 6	—	—	1	3	Nil
„ 9	—	—	1	11	Nil
„ 12	—	—	3	12	Not examined
				11	S
				10	S
„ 13	8	13	5	12	Not examined
				12	„
				12	S
				3	S
				1	S
„ 14	4	14	4	10	Not examined
				10	S
				9	S
				1	S
„ 15	4	15	4	14	Nil
				7	S
				2	Not examined
				2	S
„ 16	3	16	4	6	G
				2	S
				12	S
				5	G

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Date	Mice added	Batch No.	Mice died	Batch No. of dead mice	Bacteriological results
Oct. 17	5	17	3	11	Nil
				10	S
				12	S
,, 18	—	—	2	15	S
				13	Nil
,, 19	—	—	2	13	S
				3	Nil
,, 20	6	18	3	6	Nil
				13	Nil
				14	S
,, 21	—	—	4	2	G+S
				15	G+S
				14	S
				9	S
,, 22	6	19	2	11	S
				13	S
,, 23	3	20	3	16	G
				13	S
				13	S
,, 24	—	—	6	19	Not examined
				4	,,
				13	,,
				3	G
				4	S
				17	S
,, 25	8	21	4	3	Not examined
				4	,,
				4	S
				14	S
,, 26	—	—	3	15	Not examined
				2	G
				18	S
,, 27	8	22	3	19	Nil
				17	G
				16	S
,, 28	4	23	4	18	G
				17	S
				7	S
				2	S
,, 29	—	—	2	20	Not examined
				21	G+S
,, 30	—	—	1	7	S
,, 31	3	24	4	19	G+S
				18	Not examined
				21	G+S
				21	S
Nov. 1	9	25	5	21	Not examined
				21	G+S
				19	G+S
				17	S
				22	S
,, 2	—	—	2	21	G+S
				18	Not examined
,, 3	5	26	3	15	,,
				22	,,
				21	G+S
,, 4	—	—	1	18	G
,, 5	2	27	—	—	—
,, 6	—	—	2	21	Not examined
				22	S
,, 7	11	28	9	21	Not examined
				21	G
				21	G
				21	G
				22	Not examined
				22	G+S
				25	S

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Date	Mice added	Batch No.	Mice died	Batch No. of dead mice	Bacteriological results
Nov. 7 *cont.*				25	S
				17	S
„ 8	—	—	3	23	Nil
				23	Nil
				23	G+S
„ 9	—	—	4	21	G
				19	Not examined
				24	„
				25	G
„ 10	12	29	5	25	Not examined
				25	„
				25	G
				25	G
				22	G+S
„ 11	3	30	3	26	Not examined
				23	G
				22	G+S
„ 12	—	—	2	26	Not examined
				26	„
„ 13	6	31	4	25	„
				25	„
				28	„
				7	„
„ 14	2	32	2	28	„
				28	„
„ 15	2	33	4	28	„
				28	G+S
				31	G
				28	G
„ 16	4	34	4	16	G+S
				29	G
				28	Not examined
				28	S
„ 17	10	35	5	28	Not examined
				28	G+S
				28	G+S
				29	G
				30	G
„ 18	—	—	4	27	G+S
				29	G
				29	S
				30	G+S
„ 19	—	—	4	26	G+S
				29	G
				29	G+S
				30	G
„ 20	7	36	2	29	G+S
				32	G+S
„ 21	4	37	4	29	G+S
				31	G
				31	G
				35	Not examined
„ 22	4	38	4	27	G+S
				28	S
				29	S
				32	G
„ 23	—	—	2	29	G+S
				31	Not examined
„ 24	5	39	3	33	G+S
				31	G
				38	Not examined
„ 25	1	40	1	35	G
„ 26	2	41	3	34	G+S
				35	G
				35	S
„ 27	3	42	2	35	
				37	Nil

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Date	Mice added	Batch No.	Mice died	Batch No. of dead mice	Bacteriological results
Nov. 28	3	43	3	33	G
				34	S
				36	S
„ 29	—	—	1	35	Not examined
„ 30	—	—	3	36	„
				36	„
				38	„
Dec. 1	6	44	2	36	Nil
				38	G
„ 2	2	45	2	26	S
				39	Not examined
„ 4	3	46	3	29	G+S
				37	G+S
				43	G
„ 5	3	47	4	36	G+S
				37	Not examined
				40	G
				43	G
„ 6	—	—	3	39	G+S
				42	G
				44	G
„ 7	—	—	8	35	G
				35	G
				39	G
				39	G+S
				41	Not examined
				41	G
				42	G
				44	G
„ 8	10	48	8	29	G+S
				31	G+S
				35	G
				36	Nil
				38	G
				42	G
				43	G
				44	G
„ 9	13	49	4	35	G
				37	G+S
				45	G
				45	G+S
„ 10	5	50	4	36	G
				44	G
				44	G+S
				46	S
„ 11	2	51	2	46	Not examined
				48	„
„ 12	1	52	2	49	Nil
				49	S
„ 13	4	53	3	39	G+S
				44	G+S
				49	S
„ 14	—	—	5	46	G
				48	S
				49	G+S
				49	S
				49	S
„ 15	—	—	5	47	G
				49	S
				50	G+S
				50	G+S
				50	S
„ 16	17	54	7	47	G
				48	G
				49	G+S
				49	G+S
				49	S

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Date	Mice added	Batch No.	Mice died	Batch No. of dead mice	Bacteriological results
Dec. 16 *con'*.				49	G + S
				49	G + S
„ 17	5	55	5	48	G + S
				49	G + S
				50	S
				50	G + S
				51	G + S
„ 18	4	56	4	49	Not examined
				51	„
				54	„
				55	Nil
„ 19	—	—	3	48	G + S
				53	Not examined
				54	S
„ 20	—	—	1	48	Not examined
„ 21	—	—	1	54	„
„ 22	9	57	3	48	G
				54	G + S
				56	S
„ 23	—	—	5	48	G + S
				53	G
				54	Not examined
				55	G
				55	S
„ 24	11	58	11	47	G + S
				53	G + S
				54	G + S
				54	G + S
				54	G
				54	G + S
				54	G + S
				54	G + S
				55	G + S
				56	G + S
				56	S
„ 25	—	—	4	54	Not examined
				56	G + S
				57	S
				57	S
„ 26	—	—	4	52	S
				54	G + S
				57	Not examined
				57	S
„ 27	8	59	5	53	G + S
				54	G + S
				54	G + S
				55	G + S
				58	Not examined
„ 28	—	—	4	54	G
				55	S
				58	S
				59	Nil
„ 29	8	60	1	59	Nil
„ 30	—	—	1	58	G
„ 31	6	61	1	57	G + S
1920					
Jan. 1	7	62	4	57	G
				57	G + S
				57	S
				58	G
„ 3	4	63	3	57	G + S
				59	G + S
				62	Not examined
„ 4	4	64	2	58	S
				59	S

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Date	Mice added	Batch No.	Mice died	Batch No of dead mice	Bacteriological results
Jan. 5	4	65	3	54	G+S
				58	G
				59	Nil
,, 6	3	66	3	58	Not examined
				59	S
				60	G
,, 7	3	67	1	61	Not examined
,, 8	3	68	2	60	G
				64	Not examined
,, 9	3	69	4	60	G
				61	G
				62	Not examined
				62	,,
,, 10	3	70	3	61	Nil
				63	Nil
				66	Not examined
,, 11	3	71	1	64	Nil
,, 12	3	72	4	60	G
				61	Nil
				63	Not examined
				67	Nil
13	3	73	6	58	G
				58	G
				59	S
				60	S
				64	Not examined
				69	S
,, 14	3	74	5	58	Not examined
				60	Nil
				60	S
				63	Nil
				64	Nil
,, 15	3	75	3	70	Not examined
				70	,,
				63	,,
,, 16	3	76	6	59	,,
				61	,,
				62	,,
				65	,,
				65	,,
				66	S
,, 17	3	77	—	—	—
,, 18	3	78	1	61	G+S
,, 19	3	79	3	68	G
				72	Not examined
				74	S
,, 20	3	80	5	62	G+S
				67	G
				68	S
				69	Not examined
				71	G+S
,, 21	3	81	5	62	G+S
				65	Not examined
				67	S
				69	G
				70	Not examined
,, 22	3	82	8	58	G
				60	G
				68	G
				71	S
				72	S
				72	Not examined
				73	G
				78	G
,, 23	3	83	4	71	G
				77	Not examined
				77	G+S

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Date	Mice added	Batch No.	Mice died	Batch No. of dead mice	Bacteriological results
Jan. 23 *cont.*				81	Nil
„ 24	3	84	6	62	S
				65	S
				74	G+S
				74	S
				76	S
				79	S
„ 25	3	85	1	76	S
„ 26	3	86	7	66	Not examined
				73	G+S
				73	S
				75	Accidentally killed
				75	Not examined
				76	S
				80	G+S
„ 27	3	87	1	80	G
„ 28	3	88	4	75	Not examined
				77	G+S
				78	G
				79	G
„ 29	3	89	—	—	—
„ 30	3	90	1	79	G
„ 31	3	91	2	83	Not examined
				83	G+S
Feb. 1	—	—	2	82	S
				90	Not examined
„ 2	3	92	5	78	„
				82	S
				83	Not examined
				85	„
				85	G+S
„ 3	3	93	5	80	G+S
				81	S
				81	S
				87	G
				89	S
„ 4	3	94	4	84	Nil
				87	Not examined
				88	G+S
				89	S
„ 5	3	95	3	82	G
				90	G
				92	Not examined
„ 6	3	96	4	85	S
				87	G+S
				88	G
				90	G+S
„ 7	3	97	1	84	G+S
„ 8	3	98	1	84	S
„ 9	3	99	2	86	G
				91	G
„ 10	3	100	2	86	G
				91	G+S
„ 11	3	101	1	94	G
„ 12	3	102	2	99	Not examined
				100	„
„ 13	3	103	—	—	—
„ 14	3	104	2	88	Not examined
				93	G
„ 15	3	105	—	—	—
„ 16	3	106	3	89	G+S
				92	S
				94	Not examined
„ 17	3	107	3	97	S
				98	G
				106	S
„ 18	3	108	3	86	Not examined

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Date	Mice added	Batch No.	Mice died	Batch No. of dead mice	Bacteriological results
Feb. 18 *cont.*				96	G
				97	S
„ 19	3	109	3	95	G
				99	G
				99	S
„ 20	3	110	2	95	G+S
				96	G
„ 21	3	111	4	101	G+S
				102	G+S
				103	S
				104	S
„ 22	3	112	6	91	S
				95	S
				96	G
				98	G+S
				103	Not examined
				105	Nil
„ 23	3	113	—	—	—
„ 24	3	114	5	93	S
				94	S
				97	S
				100	S
				103	G+S
„ 25	3	115	3	98	G+S
				101	G+S
				106	G+S
„ 26	3	116	2	101	G
				105	S
„ 27	3	117	2	104	G
				107	G
„ 28	3	118	5	102	G
				106	G+S
				107	G
				110	G
				111	Not examined
„ 29	3	119	6	93	S
				108	G
				108	G
				110	S
				111	G
				112	Nil
Mar. 1	3	120	4	102	S
				105	G+S
				107	G
				115	Nil
„ 2	3	121	4	109	Nil
				113	G
				113	G
				114	G
„ 3	3	122	7	108	G
				110	S
				111	G
				112	G
				113	G
				115	G
				119	Nil
„ 4	3	123	1	119	Not examined
„ 5	3	124	1	115	G
„ 6	3	125	3	112	G
				116	S
				120	G
„ 7	—	—	1	114	G+S
„ 8	3	126	6	104	G
				109	S
				109	G+S
				114	G+S
				117	G+S

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Date	Mice added	Batch No.	Mice died	Batch No. of dead mice	Bacteriological results
Mar. 8 *cont.*				119	G+S
„ 9	3	127	3	118	G
				118	G+S
				118	G+S
„ 10	3	128	4	116	G
				117	G+S
				120	G
				121	G
„ 11	3	129	2	126	Nil
				117	G+S
„ 12	3	130	—	—	—
„ 13	3	131	3	121	G
				121	G
				127	Not examined
„ 14	3	132	1	129	„
„ 15	3	133	4	123	„
				123	„
				124	G
				128	G
„ 16	3	134	2	116	S
				133	Not examined
„ 17	3	135	—	—	—
„ 18	3	136	6	120	G
				124	G
				124	G
				126	G
				127	G
				135	Not examined
„ 19	3	137	5	129	G
				122	S
				122	S
				127	G
				128	G
„ 20	3	138	2	122	G
				130	Not examined
„ 21	3	139	—	—	—
„ 22	3	140	—	—	—
„ 23	3	141	1	132	G
„ 24	3	142	2	129	Not examined
				132	G
„ 25	3	143	1	130	G
„ 26	3	144	1	128	G
„ 27	3	145	3	123	S
				125	Not examined
				132	S
„ 28	3	146	2	133	G
				134	G
„ 29	3	147	5	125	S
				126	G+S
				130	G
				143	Nil
				145	Not examined
„ 30	3	148	3	136	G
				137	G
				144	G+S
„ 31	3	149	7	131	G
				137	Not examined
				137	G
				138	G
				139	G
				143	G
				146	Not examined
April 1	3	150	4	125	S
				131	G
				140	G
				141	G
„ 2	3	151	3	134	G

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Date	Mice added	Batch No.	Mice died	Batch No. of dead mice	Bacteriological results
April 2 *cont.*				135	Nil
				146	G
,, 3	3	152	1	138	G
,, 4	3	153	2	138	Not examined
				140	,,
,, 5	3	154	2	145	,,
				134	G
,, 6	3	155	3	140	G
				145	G
				146	Not examined
,, 7	3	156	2	139	G
				141	G
,, 8	3	157	4	136	G
				143	G
				144	G
				149	G
,, 9	3	158	5	136	G
				139	Not examined
				142	,,
				145	G
				153	G
,, 10	3	159	4	34	G
				133	G
				142	G
				153	Not examined
,, 11	3	160	2	131	G
				142	G
,, 12	3	161	7	135	Not examined
				148	,,
				151	,,
				152	G
				153	G
				154	G
				159	Not examined
,, 13	3	162	9	147	G
				149	G
				151	G
				154	S
				155	G
				156	G
				157	Nil
				157	Not examined
				159	,,
,, 14	3	163	7	20	G
				147	G
				147	Not examined
				149	G
				150	Not examined
				152	G
				156	Not examined
,, 15	3	164	1	150	G
,, 16	3	165	6	148	G
				151	G
				155	G
				158	Not examined
				158	G
				158	G
,, 17	3	166	1	150	G
,, 18	3	167	1	156	G
,, 19	3	168	4	100	G
				154	Not examined
				160	G
				162	Not examined
,, 20	3	169	4	152	G
				157	G
				159	G
				160	G

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Date	Mice added	Batch No.	Mice died	Batch No. of dead mice	Bacteriological results
April 21	3	170	1	161	G
„ 22	3	171	2	141	G
				144	G
„ 23	3	172	2	155	G
				161	G
„ 24	3	173	1	169	Not examined
„ 25	3	174	4	163	G
				165	G
				165	G
				168	Not examined
„ 26	3	175	1	165	G
„ 27	3	176	1	162	G
„ 28	2	177	—	—	—
„ 29	2	178	1	164	Nil
„ 30	2	179	1	173	Not examined
May 1	2	180	2	167	G
				173	Nil
„ 2	2	181	1	174	Not examined
„ 3	2	182	1	172	„
„ 4	2	183	4	161	G
				170	Nil
				170	G
				175	Nil
„ 5	2	184	1	173	G
„ 6	2	185	—	—	—
„ 7	2	186	1	172	G
„ 8	2	187	1	162	G
„ 9	2	188	1	174	Not examined
„ 10	2	189	6	166	„
				169	S
				171	Not examined
				172	Nil
				175	G+S
				180	G
„ 11	2	190	6	166	S
				166	G
				167	G
				171	G
				174	S
				186	Nil
„ 12	2	191	5	160	Not examined
				169	G
				177	G
				178	G
				179	Nil
„ 13	2	192	4	170	G
				183	G
				187	G
				188	G
„ 14	2	193	5	163	G
				167	G
				175	Not examined
				179	Nil
				190	G
„ 15	2	194	6	176	Not examined
				178	„
				181	G+S
				183	G+S
				185	S
				186	Not examined
„ 16	2	195	6	163	„
				164	G+S
				171	Not examined
				184	G+S
				189	S
				189	Not examined
„ 17	2	196	6	164	Nil

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Date	Mice added	Batch No.	Mice died	Batch No. of dead mice	Bacteriological results
May 17 *cont.*				168	S
				168	S
				185	G+S
				187	Not examined
				195	Nil
„ 18	2	197	6	174	Not examined
				176	S
				180	S
				181	Not examined
				184	G+S
				190	G+S
„ 19	2	198	3	177	G+S
				182	G
				188	Nil
„ 20	2	199	3	191	Not examined
				192	G+S
				194	Nil
„ 21	2	200	2	182	S
				192	G+S
„ 22	2	201	—	—	—
„ 23	2	202	—	—	—
„ 24	2	203	1	193	G
„ 25	2	204	—	—	—
„ 26	2	205	—	—	—
„ 27	2	206	2	194	G
				195	G
„ 28	2	207	1	193	Nil
„ 29	2	208	—	—	—
„ 30	2	209	1	199	Nil
„ 31	2	210	1	202	Nil
June 1	2	211	—	—	—
„ 2	2	212	—	—	—
„ 3	2	213	—	—	—
„ 4	2	214	—	—	—
„ 5	2	215	—	—	—
„ 6	2	216	2	196	Nil
				210	Nil
„ 7	2	217	1	200	Nil
„ 8	2	218	—	—	—
„ 9	2	219	1	209	Nil
„ 10	2	220	1	211	Nil
„ 11	2	221	1	198	Nil

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