THE SPREAD OF BACTERIAL INFECTION.

THE EFFECT OF DISPERSAL DURING THE PRE-EPIDEMIC STAGE, AND OF SUBSEQUENT RE-AGGREGATION.

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

(With 1 Chart.)

In previous reports (Topley, 1919, 1921 *a*, 1921 *b*, 1922) certain conclusions have been arrived at with regard to the laws which govern the epidemic spread of bacterial infection among mice. The results obtained in successive series of experiments have been so consistent, as regards their more important indications, that it has seemed justifiable to incorporate certain of these conclusions into a working hypothesis, to serve as a basis for further investigation, and to be freely amended should need arise.

This working hypothesis may be briefly stated as follows. In every case in which a bacterial parasite, possessing potential pathogenicity, and a susceptible host-population co-exist in a given area, it is probable that a condition of equilibrium is attained. It is disturbance of this equilibrium which leads to an epidemic of that specific disease to which the parasite gives rise. The conditions necessary for a disturbance of this equilibrium, in the direction of increased epidemic potential, are those which will ensure repeated passage of the parasites through a series of susceptible hosts. Such conditions may be of the most varied kind. Many of them will function simply by increasing the ease with which transference from host to host is brought about; but the one essential factor will clearly be the presence of susceptible hosts within the population concerned, in sufficient number and in sufficient concentration. It is probable that an essential element in the process is an increase in the virulence and infectivity of the parasite, but this, in its turn, depends on the presence of susceptible hosts through whom passage may be obtained, and whose resistance is itself increased when such passage occurs. When conditions favourable to the evolution of an increasing epidemic potential have existed for a sufficient time, an epidemic wave will be propagated. The subsidence of such a wave will result from the attainment of a new condition of equilibrium, in which the concentration of susceptible hosts will be greatly reduced. This reduction will probably affect both the degree of susceptibility of individual hosts and the proportion of them which possess any given degree of sus-

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ceptibility; so that we shall be left with a few fully susceptible individuals, many others possessing susceptibility of a varying grade, which can be readily overcome by a highly infective parasite, and a small proportion which are highly immune. The proportion of the host-population harbouring the specific parasite will probably be far higher than that which obtained before the original rise in epidemic potential. The equilibrium will, indeed, be established with both factors—the potential infectivity of the parasites and the immunity of the hosts—at a higher level. The conditions will therefore be particularly favourable for the evolution of a second epidemic wave, should any considerable increase occur in the susceptible population. It is probable that in a population, which has passed through a severe epidemic, the parasites are usually not in a condition immediately to infect large numbers of susceptible individuals presented to them, but that a second phase of passage with variation is necessary before the requisite epidemic potential is acquired for the propagation of a fresh wave. It will start, however, from a higher initial level, so that a concurrence of circumstances, which would have had no serious results at an earlier period, may suffice to cause a second outbreak of disease. It is probable that both the concentration and the actual number of susceptible hosts necessary for the propagation of a primary or secondary epidemic wave, have critical limiting values; since a certain number of successive passages of the virus are probably an essential precedent to this event. It would seem to follow that one of the most important factors, concerned in the initiation of the epidemic spread of bacterial infection, is the admixture of aggregates of the host-species, which are in different phases of equilibrium with regard to any particular pathogenic bacterial parasite. The conditions will be most favourable for epidemic spread, when the difference in level, at which equilibrium has been established in the two units of population before intermingling, is at a maximum, and when the numerical strength of the population in equilibrium at the lower level is large, relatively to that of the population with which it mingles. They will be least favourable, when the difference in level of equilibrium between the mingling populations is at a minimum, and when the numerical strength of the low-level population is relatively small.

No claim is made that this conception of the spread of bacterial infection is based entirely on experimental results, or that it contains any novel or unrecognised principle. In the first report dealing with these investigations (Topley, 1919), emphasis was laid on the necessity for correlating all available evidence dealing with these questions, and in this and later reports evidence derived from the observations of clinical and historical epidemiologists, as well as from those of laboratory workers, has been freely quoted. A very brief study of epidemiological literature, ancient or modern, suffices to show that most of the conceptions combined in the above hypothesis have, from time to time, gained currency among those who have written on this subject. There is little evidence, however, of any attempt to undertake careful and detailed

studies especially designed to confirm or refute the general thesis here propounded; and indeed the difficulties of obtaining such evidence in naturally-occurring epidemics among mankind may well be insurmountable. Still less does it seem to have been realised that this question may profitably be studied by that method of direct experiment, which has yielded such valuable results in other fields of scientific enquiry. For these reasons it seems probable that information of some value may be obtained by applying the experimental method to the points at issue.

The Present Investigation.

The experiments here reported were undertaken to investigate the effects of dispersal upon a population in the pre-epidemic phase of the spread of infection. It has been suggested that a certain critical value, as regards both the total numbers of susceptible hosts and their concentration, is probably essential to the occurrence of that rise of epidemic potential which precedes a wave of disease or mortality. It has also been shown (Topley, 1922), that a rising epidemic potential may be recognised by certain occurrences among the population at risk, at a period considerably in advance of the occurrence of the epidemic explosion. What will be the result of dispersing, at this stage, a considerable population into a number of small groups, so that the opportunity for many successive passages through susceptible hosts will no longer exist? The answer to this question, which appeared to be presented by the experimental results obtained, suggested the necessity of obtaining information on a further point. What will be the effect of re-combining the survivors from these dispersed groups into a single larger aggregate? Experiments bearing on this question are, therefore, included in this report.

Experiment 1. A population of 305 normal mice, which had been under observation in smaller batches for some weeks and which were apparently healthy, were collected together in a large experimental cage on May 20th, 1921. To them were added 24 mice which were presumably in such a condition of equilibrium with regard to *B. enteritidis* (aertrycke) as to give rise to an epidemic spread of infection among susceptible animals of their own species. The subsequent course of events is recorded in the Chart. This is constructed in the same manner as several previous charts, included in this series of reports. Each square corresponds to the death of a mouse. A black square indicates that a post-mortem examination clearly established the presence of infection with the organism concerned. A white square indicates that a post-mortem examination was carried out, but failed to demonstrate such specific infection. A white square with a diagonal cross indicates that the condition of the dead mouse rendered a satisfactory post-mortem examination impossible. It will be seen from the chart, that 15 mice died between May 20th and 27th. Eleven of these were from among the 305 normal mice, the remaining four were from the 24 animals forming the infective population. One of the latter, which died on May 26th, presented all the post-mortem appearances of enteric infection;

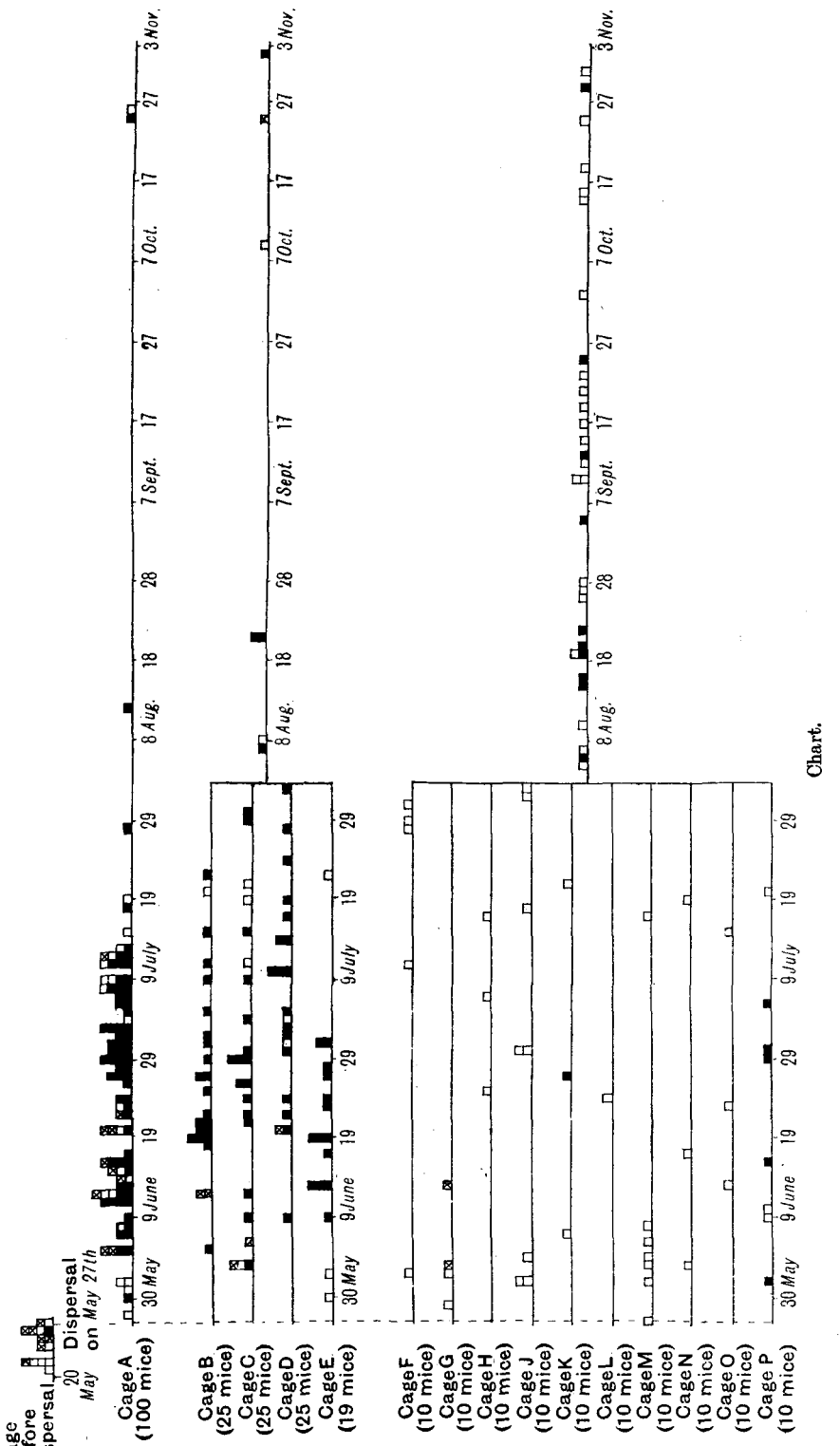

Chart.

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and agglutination tests, carried out next day, confirmed the provisional diagnosis. On that day the 314 remaining mice were dispersed as follows. The 20 mice remaining from the original infected population were removed to a separate cage. The 294 susceptibles were separated in the following way. One hundred were placed in one large cage (Cage A). Twenty-five were placed in each of three cages (Cages B, C and D). Nineteen were placed in a single cage (Cage E). Ten were placed in each of ten small cages (Cages F to P).

Comparison could thus be made between the fate of: (*a*) 100 mice which were allowed to remain in a single group, (*b*) 94 mice which were dispersed into four smaller groups, three of 25 animals and one of 19, and (*c*) 100 mice, dispersed into ten groups each containing 10 animals.

It is unnecessary to describe in detail the happenings in each of the cages, for they are clearly set out in the chart. Summarising the events between May 27th and August 3rd, we find that, by the latter date, 95 mice had succumbed out of the 100 animals that were kept together in Cage A. Of the 94 mice, which were dispersed into four groups, 85 had died. Among the 100 mice which had been divided into ten small groups, each containing ten animals, only 45 deaths had occurred. If we separate the deaths into those which were demonstrably due to the specific infection concerned, and those in which proof of this infection was lacking, the contrast becomes still more striking. The former, which may be referred to as the specific deaths, numbered 65 among the 100 mice kept as one batch, 79 among the 94 mice dispersed into four groups, and six among the 100 mice dispersed into ten small groups. It seems clear that the difference between retention in one group of 100 individuals, and dispersal into four groups of from 19 to 25, had little effect on the subsequent course of events. Dispersal into ten groups, each of ten mice, produced striking results. The total mortality was halved, and the specific mortality was reduced ten times. These results, with others, are set out briefly in Table I.

It is clear from the chart that the dispersal was carried out a few days only before the occurrence of an epidemic explosion. It will be seen that dispersal into groups of 25 shifted the epidemic wave a little to the right, that is, it occurred later in time than the wave recorded in the cage containing 100 mice. Dispersal into groups of ten, however, appears to have prevented the onset of such a wave in every case except that of the mice in Cage P; while in most cages there occurred that abnormal mortality from all causes, which we have seen to be a feature of the pre-epidemic phase. There is, indeed, a suggestion that the actual result of dispersal into these small groups has been a lengthening of the pre-epidemic phase, with an entire failure of the actual wave of specific mortality, except in Cage P.

It will be observed that in two cages only did specific deaths occur. It might, perhaps, be argued that the actual cause of the difference in the fate of the mice, according to their degree of dispersal, depended on the chance inclusion of an infected mouse among any given group. If we suppose that, at the time of dispersal, relatively few mice were harbouring the specific

parasite, there would clearly be a high probability that one or more of these mice would be included among the 100 animals, picked out at random for inclusion in the large cage, a somewhat lower probability that each of the four cages with 19 to 25 mice would be harbouring an infected individual, and a high probability that many of the cages which contained ten mice would be entirely free from infected animals.

There are, I think, many reasons for provisionally discarding this explanation. The whole of the mice concerned had, for seven days, been in intimate contact with their infected companions. During this period, as throughout the whole of these experiments, one of the daily feeds consisted of bread soaked in water, which was placed in the bottom of the cage. The

Table I.

Results of dispersal and re-accumulation of mice exposed to the risk of infection.

(Exp. 1.)

No. of mice in each group	Treatment	Mortality during dispersal (68 days)		Additional* mortality after re-accumulation (93 days)		Mortality during whole period		Final percentage of survivors
		Total %	Specific %	Total %	Specific %	Total %	Specific %	%
100	No dispersal	[95]†	[65]†	3	2	98	67	2
94	Dispersed into 4 groups: 3 of 25, and 1 of 19—for 68 days. Then re-accumulated and observed for 93 days	90·4	74·5	7·5	4·2	97·9	78·7	2·1
100	Dispersed into 10 equal groups for 68 days. Then re-accumulated and observed for 93 days	45	6	31	10	76	16	24

* The figures under this head are percentages of the number of mice originally present in each group.

† The figures in brackets indicate the mortality among the 100 mice kept in association, during the period of dispersal of the mice in the other two groups.

remnants of this bread were invariably found, next morning, to be well-contaminated with excreta. During this week of association one mouse died of enteric infection. During the 14 days succeeding the dispersal of the original population, seven mice died of the 20 survivors from the mice employed to start the spread of infection among the susceptible population. These deaths are not recorded on the chart, since at the time of dispersal these 20 mice were removed from the population to be studied. Six of these seven deaths were proved to be due to enteric infection, and it is almost certain that the majority of these mice were actively infective during the time when they formed a part of the whole population at risk. It is most probable also that some at least of the mice, whose deaths are recorded on the chart, were infected at a date previous to that on which dispersal was carried out. Under these circumstances it is in the highest degree unlikely that 80 mice could have

been picked to form the members of eight of the ten small groups F to P without the inclusion of animals which were harbouring the specific parasite. This view is considerably strengthened by the results of bacteriological examination of the faeces from these cages. The entire elimination of deaths due to specific infection was a somewhat unexpected result, and it was not until July 13th that any examination was made of the faeces in Cages F to P, with the object of recovering *B. enteritidis* (aertrycke), should it be present. In spite of the fact that this examination was delayed until this late stage, and that the recovery of this organism, from the mixed faeces taken from the cages, presents considerable difficulties, which have not yet been satisfactorily overcome, it was possible, in the course of a few examinations made between July 13th and August 3rd, to demonstrate the presence of *B. enteritidis* (aertrycke) in faeces from Cages G and J, in addition to those from Cages K and P, in which specific deaths had occurred. The probability, that the mice in these ten cages actually passed through the pre-epidemic stage of the spread of infection, is greatly increased by the events which followed their re-aggregation into a single larger group.

This re-combination was carried out on August 3rd. Cage A, which originally contained 100 mice, was left undisturbed. At this stage it contained five survivors. The survivors from Cages B to E, numbering nine in all, were collected into a single cage. The survivors in Cages F to P, numbering 55, were dealt with in a similar way, with the exception of a single buck, which, on regaining the company of his original companions, proceeded furiously to attack several mice in succession. Since it seemed certain that he would cause the death of many of his fellows if left in the cage, he was placed in isolation.

The main object of the present experiment was to observe what decrease in mortality, if any, would be produced by dispersing a considerable mouse-population into small groups during the pre-epidemic stage, and secondarily to determine whether this saving in deaths would be counter-balanced by a further outbreak of specific disease, when the dispersed units were re-combined into a single population. Had the sole object been a trial of the saving of life, which could be effected by such a procedure, it would have been the obvious course to eliminate from the re-combined population the survivors from those cages in which specific deaths had occurred, since these mice would presumably be especially liable to spread infection among their fellows. It was desired, however, to test the question whether or no the survivors from those cages, in which no specific deaths were recorded, had, during the period of dispersal, acquired any degree of immunity. For this reason, the mice from Cages K and P were included in the aggregate population made up of survivors from the ten cages F to P. The experiment was then continued for three months. During this time three mice died in Cage A, making the total mortality in this cage 98 per cent. Seven mice died among the re-combined survivors from Cages B to E, making a total of 92 deaths in a population which originally numbered 94, or a mortality of 97·9 per cent. The re-combination of the sur-

vivors from Cages F to P was followed by the occurrence of a considerable series of deaths, not collected into any kind of wave-form, but scattered over the whole period of three months, between the date of re-combination and the cessation of the experiment. The deaths were more numerous during the early part of this period. Twenty deaths occurred in the first half of the time and 11 during the latter, while the specific deaths were eight during the earlier period and two during the latter. Of the deaths which took place in the cage of re-combined mice, only one-third were due to specific infection. A comparison of the course of events in this cage, with that which may be observed in the same chart in Cages A, B, C, D and E, or which has been observed in many other experiments in which infection has been allowed to spread among a similar number of susceptible mice, shows conclusively that we are not dealing with the spread of infection among a fully susceptible population. This point is considered more fully in connection with other experiments included in this report.

The most striking features of the results recorded above are summarised in Table I. It will be seen that dispersal into groups of 19 to 25 mice produced little or no effect. Dispersal into groups of ten, on the other hand, produced the following results. The total mortality during the period of dispersal was less than half that observed in the other two groups, the specific mortality was less than one-tenth. During the whole period of the experiment, the total mortality among this group was approximately three-quarters of that in the other two groups, while the specific mortality was less than one-quarter. At the conclusion of the experiment, when the mice in the two dispersed groups had been re-accumulated into single aggregates for a period of three months, the percentage of survivors, in the group which had been dispersed into ten small units, was more than ten times that in either of the other groups.

Two other experiments on the effect of dispersal during different phases of an epidemic have been carried out; and in each case the procedure has resulted in a definite decrease in total, and especially in specific mortality. Since, however, it is intended to study in more detail the relation between the phase of the epidemic at which dispersal is carried out, and the resulting decrease in mortality, it seems best to reserve further consideration of this question for a future report.

The question of the mortality-rate, which may be expected to result from the re-accumulation of the survivors from dispersed groups, is, however, of such importance from a practical point of view, that a few additional experiments bearing on this point may be included here.

Experiment 2. On the same date as the dispersed units in Exp. 1 were re-accumulated into a single group, four batches of survivors from other epidemics of enteric infection were placed together in a single cage. The mice in these four batches numbered 7, 11, 2 and 5 respectively. During the following three months seven of these 25 mice died. Of these seven deaths, three were proved to be due to enteric infection, three mice were examined post-mortem without

finding any evidence of such disease, and one mouse was eaten by its companions. Thus, the re-accumulation of the survivors from four separate epidemics resulted, during three months, in a total death-rate of 28 per cent. and a specific death-rate of 12 per cent.

Experiment 3. In another instance, 72 mice had been received from a single dealer. They arrived in one large cage, and were at once placed in five separate cages in lots of 12 to 15 mice. During the following week several deaths from typical enteric infection occurred in each of these five cages. On August 27th, one week after their arrival, the survivors numbered 47 in all. Ten of these were set aside for another purpose, and 37 were placed together in a large cage and kept under observation. This experiment affords an example of dispersal during a very short period (seven days) in the earlier phases of an epidemic. The re-combined mice were kept under observation for 68 days. During this time 22 mice died, the total mortality being 59·9 per cent. and the specific 46 per cent.

In Table II these results, and those of several earlier experiments, are tabulated in such a way as to afford a comparison between the percentage mortality which results (*a*) when survivors from an epidemic of enteric in-

Table II.

Group No.	Composition of group	No. of mice	Period of observation Days	Percentage mortality	
				Total	Specific
1	Susceptible mice exposed to infection by survivors from a previous epidemic	100	68	95	65
2	As above	25	68	96	84
3	As above	25	68	92	78
4	As above	25	68	88	72
5	As above	19	68	89·5	73·7
6	20 normal mice and 5 survivors from a previous epidemic	25	108	92	76
7	44 normal mice and 11 survivors from a previous epidemic	55	108	83·6	76·4
8	Susceptible and infected mice in unknown proportions, but with a considerable predominance of presumably uninfected mice	124	52	89·5	54·8*
9	As above	118	60	93	Not recorded
10	As above	84	60	85·5	Not recorded
11	Mice re-combined after 7 days' dispersal into 5 small groups during the earlier phase of the same epidemic	37	68	59·5	46
12	Mice re-accumulated from survivors of 10 small groups dispersed for 68 days during pre-epidemic stage	55	93	56·4	18·2
13	Mice accumulated from 4 small groups of survivors from separate epidemics	25	93	28	12

* The low figure for the specific mortality in this experiment is due to the fact that 30 mice were eaten by their companions, and could not be examined post-mortem. The same factor operates to a varying extent in all these experiments, leading to an error in defect in each of the figures representing specific mortality, but in the remaining groups the possible error could not be significant.

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fection are mixed with considerable numbers of susceptible mice, (*b*) when mice, which have been dispersed into several smaller units during the earlier stages of one and the same epidemic, are re-combined into a single group, and (*c*) when groups of mice, which have passed through separate epidemics of the same infection, are brought together in a single cage.

A study of this table will demonstrate the following facts. If a mouse-population be formed by mingling mice, which have passed through some phase of an epidemic of enteric infection, with normal and presumably susceptible animals, in such a way that the group so formed exceeds 25 in total number, while the susceptible animals greatly outnumber their infected or immune companions, and if this mixed population be then kept under observation for a period of two to three months, the total mortality during this period is found to be in the near neighbourhood of 90 per cent. while the specific mortality is about 75 per cent. (Groups 1 to 10).

If a mouse-population be formed by bringing together the survivors of several small groups, which have been dispersed during the early stages of an epidemic of enteric infection, without adding to them any fully susceptible individuals, and the combined population be observed over a similar interval, the total mortality is reduced from 90 per cent. to between 50 and 60 per cent., while the specific mortality is still lower (Groups 11 and 12). So far as these two experiments are concerned, it will be noted that, while dispersal for a short period during the early stages of the epidemic followed by re-combination, reduced the total and specific mortality by nearly the same amount (Group 11), dispersal for a longer period during the pre-epidemic stage, followed by a similar re-combination, reduced the total mortality to about an equal degree, but produced a much greater drop in the specific mortality (Group 12). If a population be formed by accumulating mice, which have survived all stages of several different epidemics of enteric infection, and these mice be observed for a similar period, the total and the specific mortality are still further reduced (Group 13).

There is thus very definite evidence that the mortality, which was found to occur among the population formed by re-combining the dispersed units referred to in Exp. 1 of this report (see Table II, Group 12), was intermediate between that which would be expected had the survivors from the majority of these small groups been fully susceptible, and that which would have occurred had they attained that degree of immunity which is found in mice that have survived through all stages of an epidemic. These results tend strongly to confirm the conclusion, which has already been arrived at on other grounds, that the survivors from these small dispersed groups had passed through the pre-epidemic stage of the spread of infection, and in so doing had acquired an appreciable degree of immunity.

Discussion.

The ill-effects of aggregation of large masses of infected individuals, and the beneficial effect of dispersal, are common-places of epidemiology. The results of the present series of experiments would, however, seem to suggest that this principle might be pushed somewhat further. Before discussing this aspect of the question it is useful to enquire whether there are any recorded data, which afford a reasonably close parallel to the experiments which are under consideration. Such a likeness would seem to exist in the case of epidemic diseases affecting children of school age, in which school-closure is adopted as a means of preventing further spread of infection, provided that the locality affected be of such a nature that school-closure does actually bring about reasonably effective dispersal of the children concerned. It is clear that this will tend to be the case in thinly populated rural districts, and a highly instructive example of the course of events in one such case is recorded in a report by Power (1883) on an outbreak of diphtheria at Pirbright in Surrey. The report itself must be consulted for the full details and circumstances of the outbreak, but the salient points may be noted here. The outbreak started in April, 1882, although there had been a few scattered cases during the earlier part of the year. Between May 16th and November 25th the school was thrice closed and thrice reopened, being closed again on the latter date. Each closure led to a marked decrease in the incidence of diphtheria among children of school age, while each reopening led to a fresh increase; but the increase on reopening never brought the incidence back to its original figure, and the successive reopenings appear to have exerted a diminishing effect. It is hardly necessary to stress the similarities between these happenings and those recorded in the experiments under discussion.

It seemed possible that procedures, based on the principle of dispersal during the early stages of an epidemic, might already be in vogue in dealing with epidemics among live-stock, where methods of segregation are so much more easily enforced than among human populations. Being insufficiently acquainted with the literature of the subject to discover these facts for myself, I have enquired from those with the requisite knowledge concerning the measures which are commonly employed among agriculturists in attempting to limit the ravages of an infective disease, once it has declared its presence amongst a collection of live-stock. I would again express my indebtedness to Sir John M'Fadyean and Sir Stewart Stockman in this country, and to Dr Simon Flexner and Dr Theobald Smith in America, for their kindness in answering my enquiries. From the information which I have obtained, it would appear that the methods employed, or officially recommended, are limited to the isolation or slaughter of infected animals, the detection of carriers and atypical cases, where suitable means exist for this purpose, and the segregation or slaughter of the animals thus indicated as a source of danger. Where adequate means are available for producing a temporary immunity in the unaffected

members of a herd, this procedure is adopted in addition to the elimination, by isolation or slaughter, of the infected animals. When experience shows that the epidemic in question is of such a nature, that it will probably spread widely among a herd in spite of all precautions and may constitute a danger to other herds in the neighbourhood, it is customary, in some cases, to slaughter the entire herd under Government orders and with adequate compensation. All these procedures are, of course, combined with such measures of disinfection as experience has shown to be most trustworthy. With methods of quarantine, designed to prevent the spread of disease from one herd to another, or from one district to another, we are not here concerned.

In the light of the results obtained in the experiments recorded above, it would, perhaps, be of value tentatively to apply the principles suggested by them to the control of such epidemics, and to test the effect of dispersal into small groups, at the first sign of an outbreak of infective disease, followed by re-accumulation into groups of a more manageable size after a certain interval. Such field-experiments would afford the most useful information, if carried out on large animal populations. The most suitable conditions would, perhaps, obtain in connection with the infective diseases of poultry, and it seems possible that it is among this class of live-stock that such measures would possess their greatest utility, should further experience confirm the hope that an appreciable decrease in mortality might be attained by procedure along these lines.

It is, indeed, largely because it seems probable that observations carried out under field conditions may serve to confirm or refute the conclusions drawn from laboratory experiments, that these preliminary investigations are reported at the present stage.

CONCLUSIONS.

1. If a mouse-population, which has been exposed to the risk of infection, be dispersed into several *small* groups during the pre-epidemic stage, the total mortality will be far less than if the animals be retained as a single large group. The specific mortality will be reduced to a still greater extent.

2. During the period of dispersal, the mice forming the small groups will, in most cases, have passed through an extended pre-epidemic phase of the spread of infection. In so doing they will have acquired an appreciable degree of immunity.

3. If the small groups be later re-combined into a single aggregate, further deaths will occur; but the total mortality among a group of mice, which has been dispersed and then re-accumulated, will always be less than among a similar group, which has been retained from the commencement as a single unit of population. The specific mortality will generally show a still greater reduction.

It remains for me again to express my thanks to my colleagues, Dr H. B. Weir and Dr G. S. Wilson, for their assistance in this investigation.

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