SOME ASPECTS OF HERD IMMUNITY.¹

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Some years ago, when discussing the concept of herd immunity, I included among effectively immune herds those that owed their resistance, not to the individual immunity of their constituent members, but to the social or biological structure of the herd as such. This drew from a kindly critic the objection that such a definition would cover any community that happened to be blessed with an efficient medical officer of health, and would hence give to the term "immunity" a twist not justified by its ordinary scientific use. I still think that the restriction of the concept of herd immunity to those instances in which some or all of the herd members are themselves immune would exclude some of the most important mechanisms on which the resistance of a herd depends, and among those mechanisms it seems to me reasonable to include the medical officer of health, provided that his activities produce results of a particular kind.

It is important to get our definitions clear, and I would suggest the following to cover herd immunity of all types:—

The immunity of any herd in relation to any infective disease may be expressed inversely in terms of the rates of morbidity or mortality induced by the exposure of that herd to the risk of infection with the causative organism of the disease in question.

It will be noted that this definition excludes those societies that are kept free from any given disease by the complete exclusion of the causative parasite, i.e. by successful quarantine. We are, indeed, applying to the herd the same test of immunity that we apply to the individual. It must be able to withstand exposure to risk. With herds, as with individuals, there are, of course, all gradations between complete immunity and complete susceptibility, and we are almost always dealing with relative, not with absolute, values, our standard of comparison being the behaviour of an average herd, or group, or individual when exposed to infection with the organism concerned.

Adopting this general definition of herd immunity, we may compare two kinds of herd structure, both leading to increased resistance, but depending on very different mechanisms.

Taking first the type of immunity that is dependent on the social or biological structure of the herd, but is independent of the individual

immunity of its members, we may note that it may be determined by a wide variety of factors, the effect of which is to prevent the generalization within the herd of any local focus of infection. An immunity of this kind is seldom narrowly specific in its action. It tends to be effective against epidemiologically differentiated groups of diseases—water-borne infections, infections carried by insect vectors, and so on, rather than against particular parasites. It is shared by individual members of the herd only so long as their herd-membership continues.

To get our minds quite clear on these points we may consider a few illustrative examples.

One excellent example is the immunity of the English herd to plague. Englishmen abroad are fully susceptible to this disease, but Englishmen at home can view its introduction into this country with complete equanimity. It has in fact been introduced, and nothing of any significance has happened. The intriguing story of plague in East Anglia between 1906 and 1918 has recently been told by Greenwood in his book on epidemics and crowd diseases. Here we need only note that a widespread infection of the rat population existed, but the plague deaths in man numbered only seventeen in twelve years. Clearly, plague can no longer spread among us; and this is almost certainly due to the fact that the relations between man, the rat and the flea, are no longer those that the bionomics of the disease demand.

The English herd is almost immune to malaria, and for analogous reasons. It is, under its present conditions, almost certainly immune to typhus.

These are all instances of diseases borne by insect vectors. Our partial immunity to enteric fever affords an example in which this factor is not involved. The standardized death-rate from this disease in 1870 was 385 per 100,000 living at all ages: in 1931 it was six. Yet typhoid and paratyphoid bacilli are still with us, as is witnessed by many recent reports of their isolation from sewage in widely-separated areas.

There is no mystery as to why enteric fever has fallen from an important to a relatively trivial cause of disease and death. Adequate conservancy systems and adequate water supplies have done almost all that was necessary. If those local authorities that have not yet learned this lesson would put their houses in order, and if our administrators could be brought to realize that raw milk is not a commodity that can safely be handled and distributed, the six deaths per 100,000 of 1931 would soon approximate to zero.

The other type of herd immunity with which I wish to deal is determined by the individual immunity of some or all of the herd members; and we may here confine our attention to those instances in which this individual immunity is of the kind that results from natural infection or artificial immunization. Such immunity depends on antigen-antibody reactions of various kinds, and is narrowly specific in its action, protecting against infection with a particular bacterium or virus, rather than against a clinically or epidemiologically differentiated disease.
It would be superfluous to give illustrative examples. The facts are too well known to you all. It may, however, be worth while to consider briefly the way in which this type of immunity acts in herds that have no structural immunity of the kind previously considered.

The experiments that Professor Greenwood and I have carried out during the past twelve years or more have led us to certain tentative conclusions on this particular problem. These conclusions do not differ from those that have been reached by many epidemiologists as the result of observations in the field; but they may serve to add precision, and to exclude some of the hypotheses that have, from time to time, enjoyed a certain vogue.

Our experimental herds of mice differ in important respects from any natural herds of men or animals. They have been formed by bringing together a certain number of mice infected with the disease under study and a larger number of normal mice. They have been maintained, often for several years, by adding each day a constant number of normal mice. Three mice a day has been the usual rate of addition; but in certain experiments we have added smaller or larger numbers.

If we follow the events in one of these herds in terms of secular time, noting the number of deaths that occur each day, calculating the mortality rate and expressing this in the usual graphical form, we find that there is usually a wave of mortality within a few weeks of the assembly of the herd. During the first few months there are often a number of well-separated waves of mortality, but later these tend to become fused and irregular, except when the rate of addition of normal mice is very low. The tendency seems to be towards a relatively steady death-rate, and this tendency is most marked when the rate of daily additions is highest. The indication is that with a very high immigration rate a steady death-rate would actually be obtained; and, since the immigration rate is also constant, this means that the total population will also reach a constant level, so many mice being added in a unit of time and the same number dying. A typical experience is illustrated in fig. 1. So far as we can judge from our experience, the death-rate from any given disease appears to be independent of the rate of addition of susceptibles, so that the level at which the population becomes constant depends solely on the rate of immigration.

This state of epidemic equilibrium, which is quite unlike anything that happens in the natural world, would, so far as our limited experience can be taken as an indication, last indefinitely, so long as the herd was subjected to a constant rate of immigration of susceptibles and shielded from any violent environmental changes. This observation is, we think, of some theoretical importance, since it indicates that the epidemic process, when fully established under conditions that allow free spread of infection, has no inherent factor that imposes periodicity, or, indeed, any wave-like movements of mortality. The waves and periodicities that we observe in
natural epidemics must, therefore, be imposed by variations in those factors that, under the conditions of our experiments, we are able to keep constant.

A more detailed and informative picture of what is happening in our infected herds is, however, obtained by studying events in terms of life-table time instead of secular time, that is, by noting the behaviour of mice that have lived ten, twenty, thirty, forty days, and so on, in the herd under the average conditions persisting throughout the months or years of a particular epidemic, instead of observing the behaviour of the whole herd, or of any particular group within it, at successive intervals of time from the beginning of the experiment onwards. We can use various measures in assessing the behaviour of mice of different cage-ages. One of the most convenient is the expectation of life—the average number of days that mice which have lived for $x$ days in herd survive after day $x$. We have used a limited expectation of life, fixing the limit at sixty days, because the use of the unlimited expectation would give an undue weight to those relatively few mice that live for very long periods. To provide ourselves with a standard of comparison we have carried out a control experiment in which a herd of normal uninfected mice, housed in the same kind of cage and fed on the same kind of food as our infected herds, was recruited by the immigration of three normal mice a day. Under these conditions the average expectation of life limited to sixty days is approximately fifty-eight days, and we may take this as a measure of the average risks of herd life apart from the existence of any epidemic prevalence. The limited expectation of life of normal uninfected mice is not absolutely constant throughout herd life. It is slightly below the average during the first few weeks in herd, slightly above the average from the sixth week or so onwards. This is probably because mice are sturdy nationalists, very suspicious of all new immigrants, and each new-comer is at an appreciable risk until he has established his position as a herd member.

In fig. 2 are set out in graphic form the limited expectations of life at different cage-ages, for the normal uninfected mice, for two herds infected with mouse typhoid, for a herd infected with pasteurellosis—a disease somewhat resembling pneumonic plague—and for a herd infected with a virus disease, ectromelia. It will be noted that mice on entry to an infected herd have about half the normal expectation of life. This disadvantage increases until about the tenth to twentieth day, the exact period varying from one disease to another. At this stage of minimal expectation of life, which clearly corresponds to the average time taken by new entrants to develop the disease, mice in infected herds have between a quarter and two-fifths of the normal expectation. Thereafter the position of the survivors steadily improves. Those mice that have survived in herd for fifty days have about 70 per cent of the normal expectation; those mice that have survived for one hundred days have about 80 per cent. The exact figures vary a little from one disease to another, but not to any significant degree.
For reasons which it is impossible to set out in detail here, we believe that this increase in the resistance of surviving mice is, in the main, the result of active immunization induced by sublethal infections contracted during the early periods of herd life. We have, for instance, evidence that some 50 per cent of all immigrants are infected within two weeks of entering an infected herd; some 80 per cent within four weeks. Some

![Graph](https://example.com/graph.png)

**Fig. 2.**

- Normal uninfected mice (all deaths)
- Mouse Typhoid A6 (specific deaths)
- Mouse Typhoid A3 (specific deaths)
- Pasteurellosis P3N (specific deaths)
- Ectromelia Ect.l. (all deaths)

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part of the high average resistance displayed by old survivors is undoubtedly due to the selection of innately resistant mice by the death of their more susceptible companions; but for reasons that we have set out fully elsewhere we believe that genetic factors are of less importance than natural immunization.

Since resistance increases with length of survivorship in herd, the death-rates will clearly differ at different cage-ages. In Table I are set out the death-rates at cage-ages for two epidemics of mouse typhoid, which will serve to illustrate the general trend in all our experiments. In constructing our tables we use an actuarial death-rate, the probability of dying within the next five days. For the benefit of those who find percentage mortalities easier to follow than long decimal figures, I have in this table multiplied the \( \frac{5}{2} x \) figures by 100. These tell, in another way, the same tale as the change in expectation of life illustrated in the graph. The older survivors are subject to a relatively low rate of specific mortality, but it never reaches zero, just as their expectation of life never attains to the normal level. This clearly means that the immunity attained is never absolute; all mice, in the long run, tend to die of the reigning disease. Were this not so, the invariant population with a steady specific death-rate suggested by our secular graphs could not be attained. There would be a piling-up of completely immune mice, the specific death-rate would fall, and stability of the population would only be reached at the point where senility played the major rule as a cause of death.

<table>
<thead>
<tr>
<th>Cage-age in days</th>
<th>Mouse Typhoid (6)</th>
<th>Mouse Typhoid (3)</th>
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<tr>
<td>0</td>
<td>1.4</td>
<td>0.8</td>
</tr>
<tr>
<td>5</td>
<td>4.8</td>
<td>3.0</td>
</tr>
<tr>
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<td>9.9</td>
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</tr>
<tr>
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<td>14.6</td>
<td>16.4</td>
</tr>
<tr>
<td>20</td>
<td>24.1</td>
<td>32.4</td>
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</tr>
<tr>
<td>100</td>
<td>3.3</td>
<td>6.4</td>
</tr>
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</table>

In the light of these observations we may consider again the picture given by our secular graphs and fill in some of the details. When an infected herd is formed there is a rapid spread of infection, associated within a few weeks with a wave of mortality. The majority of the new entrants are infected soon after entry to the herd; half of them within a fortnight, 80 per cent or more within a month. During the earlier stages of the epidemic the mice at risk are in part being killed by the prevailing
disease, in part being immunized by sublethal infections. This early stage is marked by a widely fluctuating death-rate, or in some cases by separated waves of mortality. Later, as the total population increases, it becomes differentiated into sub-groups of varying cage-age, and consequently of varying resistance. Finally, a condition of equilibrium is attained, in which a steady average death-rate, derived from different death-rates operating on the different cage-age groups, combines with a steady rate of immigration to produce an invariant total population.

This seems to be what happens, under the particular conditions of our
ECTROMELIA. LIMITED EXPECTATION OF LIFE (60 DAYS) OF IMMUNIZED AND CONTROL MICE

Fig. 4.
experiments, when an epidemic is allowed to run its natural course. It is of greater practical interest to inquire whether we can interfere in such a way as to lower the death-rate and increase the expectation of life. One obvious method of interference is to decrease the risk of contact infection. That method we hope to try in the near future. We have not tried it yet because it has taken many years to get a reasonably accurate and detailed picture of what happens when the risk of infection is maximal, and until that picture was obtained we had no adequate standard for comparison.

Another obvious method is artificial immunization. We might hope, by immunizing mice before entrance to the herd, to place them at once in the position of the more resistant survivors, and so increase the average expectation of life. If we were very optimistic we might even hope to render them completely immune, and so bring the epidemic to a close. That method we have tried, using in the case of mouse-typhoid an ordinary killed bacterial vaccine, and in the case of ectromelia a formalized attenuated virus. The results are shown in figs. 3 and 4. Each graph shows the limited expectation of life at different cage-ages for: (a) The immunized mice; (b) for a control group of non-immunized mice added to the same infected herd; and (c) for our standard herd of normal-non-infected mice.

The result of immunization against mouse-typhoid was disappointing. It is true that, at all periods of herd life, the immunized mice fare better than the controls; but at no period does their expectation of life approach the normal. Moreover, we have clearly failed to place our vaccinated mice in the same position as the old survivors that have passed through the experience of active immunization and selection. The curve for the immunized mice is of the same form as that for the non-immunized controls, falling to a minimum about the twenty-fifth day and then rising with increasing herd experience. It simply runs at a higher level. This is not a very effective immunity, and it was not surprising to find, in another experiment, that the effect of immunizing all entrants to a herd was simply to lower by a little the average death-rate, and increase the average survival time. The epidemic continued for a year or more and showed no sign of abating.

The graph showing the results of immunization against the virus disease, ectromelia, presents a very different picture. We have not raised the resistance of our immunized mice to a point at which they are indifferent to the prevailing disease, but they have, on the average, about 85 per cent, of the normal expectation of life. Moreover, we have here succeeded in placing our immunized animals on the same level as the old survivors of the herd. The curve for the immunized mice approximates to a straight line. It does not follow the curve for the non-immunized controls; it follows that for normal uninfected mice, but on a slightly lower level.

If, now, we turn from mice to men, from our cages to the world outside them, have these observations any significance for those who have to deal
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with the practical problems of hygiene? My colleague, Greenwood, and I are very loath to venture far as yet on this dangerous ground. The conditions in our cages are very unlike those in human communities. We hope to be able to speak with a little more confidence on such points as these in another ten years or so, when we have studied the effects of varying the risk of contact infection.

For the moment we would confine ourselves to a few tentative conclusions.

We think that all our experience accords with the view that natural immunization by clinical or subclinical infection, combined with the rate of accumulation of susceptibles in a community, is the most important single factor in determining the form of the endemic-epidemic prevalence of a disease that is provided with ample channels of natural spread.

In regard to artificial immunization we should regard our results as in accord with the common experience that vaccination against a virus disease tends to be far more effective than vaccination against a bacterial disease of the invasive type. We have as yet had no opportunity to study a bacterial disease of the toxemic type, analogous to diphtheria or scarlet fever in man. We should, indeed, regard our experience with immunization against the virus disease, ectromelia, as highly promising. The experiment needs repetition because, towards the end of the epidemic, the vaccinated mice suffered a considerably increased mortality. The great majority of those that died showed no signs of ectromelia; but their deaths could not be ascribed to any known cause, so that we must maintain an open mind on this point until the experiment has been made again. If the results accord with those of the earlier part of the previous epidemic, we should regard the immunity as highly effective.

Any additional proof of the efficacy of immunization against virus diseases is welcome. It strengthens the faith of those of us who believe in smallpox vaccination, whether we are supporters of infant vaccination en masse, or of vaccination of communities in the presence of an incipient epidemic. Moreover, we now know, thanks to the work of Laidlaw, Andrewes and Wilson Smith, that influenza is a virus disease, and we have two strains of the virus being propagated in ferrets and mice. It cannot, one would guess, be long before we are in a position to immunize effectively against this disease; and when that is achieved it will be one of the major victories of preventive medicine.

In regard to our experience with mouse typhoid we should not adopt a wholly pessimistic view. It is true that the protection afforded was, as judged by this trial, of a low order, and that if this were the best result that could be expected in man grave doubts would arise as to the efficacy of anti-typhoid vaccination. But man is not exposed to the continuous risk of massive infection that our mice encounter; and it is quite possible that a degree of immunity that avails little under conditions of maximal stress may afford an effective protection when the risk of infection is greatly
diminished. There is, indeed, no real discrepancy between our findings and the records of anti-typhoid inoculation in the field. No one would claim that typhoid or T.A.B. vaccine affords absolute protection against disease or death. The figures of the Anti-typhoid Commission of 1913 show an attack-rate in the inoculated about one-sixth that in the un-inoculated. The disease was greatly diminished in frequency, but it was not eliminated.

In so far as we can argue from mice to men, the tentative conclusion that we should be disposed to draw from our mouse-typhoid experiments is that, in the enteric group of diseases, the effect of artificial immunization is not such as to allow us to dispense with the type of structural herd immunity to which I referred in the opening section of this paper. In the Boer War the incidence of typhoid fever was 105 cases per year per thousand of strength. In the Great War of 1914-1918 it was, among the British armies in France, 2.35 cases per year per thousand of strength. If the Great War had been fought under the sanitary conditions of the Boer War, anti-typhoid inoculation would almost certainly have reduced the incidence below the terrible figure that was actually experienced in South Africa thirty-five years ago, but it is, at least in our view, very unlikely that it would have approximated to the almost negligible figures of 1914-1918.

Another lesson that we should draw from our experience with mouse typhoid is that we should not rest satisfied with our present methods of active immunization against the enteric group of diseases. While artificial immunization against ectromelia accomplished all that natural immunization was able to effect, this was not the case with mouse typhoid. The vaccine employed fulfilled all the conditions that would commonly be regarded as essential for an effective antigenic stimulus, but there can be little doubt that something was lacking, either in the reagent employed or in the method of its application. Professor Raistrick and I are now attacking this problem on its chemical side in the hope of evolving a more effective antigen. Wherever else the methods of experimental epidemiology may fail, they at least allow us to put any prophylactic reagent to a trial so severe that any reagent that proves effective under the test conditions may be relied on to prove effective in the field.

Finally, I would turn once more to the point at which I started. The type of herd immunity that is independent of individual immunity is, if it can be established, so effective, and demands so little interference with the individual citizen, that procedure along these lines should be adopted wherever possible. It is, however, impossible to foresee a time when any modification of herd structure will impose an effective barrier to the spread of all types of infection within the human herds with which we are concerned. Whether other members of this Congress can think of any practicable method of preventing the spread of disease by so-called "droplet" infection, I do not know; but I can think of none. In this
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great group of diseases, at least, the auguries are that artificial immunization will, for many years to come, form our first line of defence. I think that here, as elsewhere, the method of the experimental epidemic will yield knowledge of real value. But I think, too, that progress will be much slower than it need be if the experimental outlook is confined to the laboratory instead of being extended to the field.

As an example, I would cite the instance of whooping cough. It is an important killing disease. Laboratory knowledge has reached a stage at which a *prima facie* case exists for the probable effectiveness of a vaccine prepared with due regard to the antigenic structure of the strain of organism employed; but the reports from the field are conflicting. Until we know the truth of the matter it would be very unwise to embark on a campaign of wholesale immunization; and we can only learn the truth by field trials, properly planned and properly carried out. Surely it should be one of the major preoccupations of an efficient public health service to plan trials of this kind, to watch for hopeful prophylactic methods as they emerge from the laboratory, to submit them at the earliest possible moment to an adequate and critical test, to reject them if they prove ineffective, to adopt them if they fulfil the necessary requirements. This stage of adequate field trial, conceived in a frankly experimental spirit, presents, I know, special difficulties to the administrator. But it is, perhaps, the most important link in the chain that leads from an observation in the laboratory to successful prophylaxis in the field.