Observations

ON THE

FACTORS DETERMINING THE DIFFERENCE
BETWEEN AN EPIDEMIC OF ONE DISEASE
AND THAT OF ANOTHER *

BY

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A critical examination of the title alone of this discussion is enough to show how hard a task we shall have to be precise. We should all find it difficult to devise a better title and yet it is almost as naïve as the question of a child to its elders. What is a disease? What are we to understand by the term epidemic? In the record of infectious diseases which is prepared in the division of epidemiology of the London School of Hygiene and rendered weekly to the Medical Intelligence Division of the Ministry of Health, one item is enteric fever. Week by week we compare the recorded incidence with what we call the expected incidence—namely, an average based on the experience of 1922-30. In this work no distinction is attempted between typhoidal and paratyphoidal infections because, from the administrative point of view and the etiological point of view of an epidemiologist, whose unit of observation is a group, not an individual, these biologically distinct infections lead to the same result. For the purpose in view they lead to but one disease, as we say. But, from the standpoint of prophylactic immunization, to bring together typhoidal and paratyphoidal infections would be ridiculous; from *that* point of view, they are two diseases. With still greater boldness, and the same practical justification, we do not distinguish between the influenzas of different years, although, in many respects, these are as different as phenomena can well be. In fact, we cannot provide a criterion of difference, or sameness, which will be satisfactory to all users of the term "disease." Similarly we cannot define epidemic adequately, any more than the victim of the sophist could tell when a heap of stones from which one stone at a time was subtracted, ceased to be a heap of stones. Yet, when this is said, we all feel that dialectical difficulties should not be allowed to frighten us from discussing a question which has interested members of our profession for thousands of years.

HISTORICAL AND STATISTICAL METHODS OF STUDY

The epidemiology of classical and Hellenistic Greek science was logical and self-consistent. According to Galen, there were three factors—two innate or acquired aptitudes of the body, the temperamental and procatartical; and one external, the atmospheric katastasis. This latter determined the quality, and the two former the severity, of an epidemic.

"So often as the katastasis of the atmosphere departs from its proper nature into the hot and humid, pestilential diseases must needs arise, yet will those chiefly be affected who were beforehand saturated with excrementous moisture while those who labour moderately and are temperate in diet remain refractory to such diseases." (*De Februm Differentiis*, I.)

Translating from an obsolete notation into one more congenial to our habits of thought, Galen's view is that

* Made in opening a discussion in the Section of Pathology and Bacteriology at the Annual Meeting of the British Medical Association, Eastbourne, 1931.

it is rather the condition of those exposed to infection than the nature of the infection which determines the difference, in the sense of our title, between one epidemic and another. He would explain the difference between the influenza of 1918-19 and that of 1931, not in terms of the katastasis, or, as *we* should say, specific differences of the infecting agent, but in terms of contrasting resistances.

Sydenham, on the other hand, enormously extended the sphere of the katastasis. He freed it from the naïve implications of such terms as hot, cold, moist, and dry; in modern speech, and popularized, if he did not actually invent, the doctrine of the epidemic constitution. He would have held that the influenza of 1918-19 differed from that of 1931 *essentially*, just as the port vintage of 1887 differed essentially from the vintage of 1897, because the complex of essential biological and cosmic factors had changed.

To some this will seem no more than archaeological triviality. What in the world have we, in the year of grace 1931, to do with Galen and Sydenham? The answer is that we are still wrangling about *their* problems, changing nothing but the notation. Some hold that the proper way to find out the truth is to do what Sydenham advised—to go back to Hippocrates's method and write the history of the epidemic constitutions not of Thasos but of the civilized world. Those who give this advice certainly resemble Sydenham in one respect, namely, in despising contemporary methods of research. They have no more use than Sydenham himself for statistical methods of study, except in so far as these methods can be directed against the abhorred bacteriologist. They say, quite rightly, that the statistical method is limited and selective; that it selects some only of the possible objects of study and these, perhaps, not the most important. I respect the ideals of epidemiologists of this class: I share their enthusiasm for medical history: I agree that there are many more things in heaven and earth than are recorded in the annual reports of the Registrar-General, or are amenable to the calculus of correlation. I can even bring myself to believe that Ballonius, Sydenham, or some wise man whose works I have not read, did really possess the key to all the mythologies of epidemics. But although we owe to students of history valuable criticisms, their creations have been less valuable. Perhaps Ixion was not the last person who mistook a cloud for the queen of heaven and engendered a race of centaurs.

On the other hand, the laboratory bacteriologist falls into the opposed error of over-simplification. His little world of individual experimentation is a very imperfect model of the world of men and women, and the inferences from the former extended to the latter have often made him fair game of the epidemiologists who have studied "real" epidemics.

In my view, a *via media* between the over-elaboration of the disciples of Sydenham and the over-simplification of the academic bacteriologists must be chosen. We must, by a deliberate limitation of the field of observation, try to discover which of the vast number of possibly influential factors are likely to repay study in the world of "real" epidemics. Within that limited field we must use the methods of statistical description which, although they have not enabled us to solve the problems of epidemicity, have at least been valuable instruments of sanitary administration. That is the case for experimental epidemiology.

The Section will, I think, be more interested in the bacteriological and immunological aspects of work in this field than in its purely statistical features. I shall therefore merely summarize what I believe to be probable epidemiological conclusions before making way for those more competent to deal with other sides of the work.

SCOPE OF EXPERIMENTAL EPIDEMIOLOGY

Experimental epidemiology is an attempt to simplify the study of general epidemiology by (1) limiting the number of variable factors (for example, by rigorously excluding from the herd under observation all but one extraneous infection); (2) taking as the object of study a herd of short-lived animals, so that the time-scale of observations is magnified. These advantages are purchased, of course, at a heavy price. We can undoubtedly control many of the conditions of life of a herd of mice; but, on the other hand, our knowledge of the social biology of mice is more scanty than our knowledge of the social biology of men, and the conditions of life we can secure for our herds are no doubt very different from those appertaining to a colony of mice living, not in Gower Street, but in the sylvan world of mice. The application of our results to the elucidation of the problems of human epidemiology is therefore analogical at two removes. There is a gap between our mice and mice in general and a still wider gap between mice in general and men in general. We are, however, no rasher in this way than other experimental biologists are forced to be.

OUTLINE OF INVESTIGATION

A large majority of our studies have been of herds deliberately exposed to infection by either *Past. muriseptica* or *Bact. aertrycke*. Experimental herds have been assembled by bringing together naturally infected animals (survivors of previously infected herds) and healthy animals or inoculated and healthy animals. The herd so formed has been recruited either from healthy animals, healthiness being guaranteed by an extremely rigid process of quarantine, or from animals which have fulfilled other specified conditions. The results observed have been summarized or described in various ways. For the main purposes of this discussion, I shall use two. (1) The daily death rate at ages, which is precisely equivalent to the death rate at ages of our human vital statistics, save that age, in our studies, is cage age; entrance to the herd is, for our purposes, birth. (2) The expectation of life limited to the next sixty days. In human vital statistics, the expectation of life at any age, say 10 years, limited to any period, say 60 years, is the average number of years of life lived by persons aged 10 during the next sixty years of existence. All those who survive to 70 will be credited with sixty years each, all those who die between 10 and 70 will be credited with the number of years they survived. For mice, which live, perhaps, a thirtieth of the normal span of human existence (much less in infected herds) sixty days from entrance reduces the population of contemporary entrants to 10 per cent., or less, of its original strength, so that this measure, although subject to the objection which can be urged against all concise statistical measures, namely, that it ignores important details, is a comprehensive one. It is better than the complete expectation of life, that is, the average survivorship to the end of life, because this may be greatly influenced by the fates of a small number of exceptionally hardy individuals.

SECULAR FEATURES OF HERDS

Before taking up the points to which I wish specially to direct your attention, I shall say a word on the ordinary secular features of the herds. Our experience is that the secular mortality of a herd undergoes vicissitudes graphically similar to what is seen in the mortality statistics of a human community observed over several generations. We have been no more successful than have students of human mortality in discovering a real "law" of periodicity and, unlike some of the students of experimental

epidemiology in other countries, we have not been able to satisfy ourselves that either seasonal variations or modifications of the diet determine the epidemiological history of the herd, under the conditions existing in our experimental series. We have, however, satisfied ourselves that, once a herd has been infected with a specific *materies morbi*, the resultant disease will maintain its footing in the herd for many generations, emerging after periods of quiescence which, in terms of human generations, would be very long, provided the herd be regularly recruited from healthy, non-immune stock. We also think that reduction in the rate of additions usually—although not invariably—diminishes the secular rate of mortality and leads to the substitution of an irregular zig-zag curve of mortality for a high and relatively constant rate.

AGE AND MORTALITY

Passing now to age and mortality, some idea of the nature of events is conveyed by the comparison of the limited expectations of life at entrance of (1) mice under the most favourable conditions; (2) mice under "ordinary" infected conditions, and (3) mice under "optimum" infected conditions. By the first class I mean mice living in a herd under the same conditions as the experimental herds but not exposed to infection. Their expectation is fifty-seven days. By the second I mean the ordinary entrants to herds exposed to aertryckal infection. Their expectation of life is twenty-five days. By the third I mean mice admitted to the last-mentioned herds after artificial immunization by the methods which proved most effective. Their expectation of life is thirty-two days. The maximum span is sixty days, so that the first class enjoyed 95 per cent., the second 42 per cent., and the third 53 per cent. of the maximum possible.

If we consider the course of mortality with age of each of the three types, the results are as follows. For the first class our data are not complete enough to permit of any quite conclusive inference, but it seems probable that "healthy" mice conform reasonably closely to what has been called Gompertz's law of mortality, namely, that the force of mortality (for present rough purposes we may say rate of mortality) increases geometrically with age. It is at least certain that such mice do not exhibit an increase of mortality to a maximum early in life, that is, at an age at all comparable with the epoch of maximum in the second and third classes (see below). These classes contrast with the first in showing a regular and rapid increase of mortality with age to a maximum between the fifteenth and thirtieth day of cage life (the maximum is later in aertryckal than in pasteurellal infections); from this maximum the rate descends more or less smoothly to a level which is thereafter maintained; the trend from about the fortieth to the fiftieth day of cage life oscillates about a parallel to the axis of zero mortality, parallel to that axis but much above it. The maximum of the third class is much lower than that of the second, but sooner or later the curve of the former rejoins that of the latter and, had we only under examination the rates of mortality at ages over 50 days, we should be unable to distinguish the two sets. The advantage derived by pre-immunization is in respect of exposure to risk early in cage life. That ultimately the two curves of mortality should approximate is intelligible, but it might, perhaps, have been hoped that the ultimate rates of mortality of survivors should approximate to those of mice not exposed to the infection, that by virtue of active immunization and survival of the fittest we should eventually produce a population of, in a Pickwickian sense, elderly mice fit, like Macbeth, to laugh to scorn the specific dangers of the herd. As in Macbeth's own case, the dangers are rather more complex than appeared.

SELECTION AND IMMUNIZATION

A first point of interest is how far the relative protection acquired by survivors beyond cage age 30 is a consequence of survival of the fittest or of active immunization. We have carried out a series of experiments to determine that question. The method was to recruit a herd from two sources. One source was ordinary, healthy, quarantined immigrants: the other was a set of mice which had survived varying periods in a herd within which the infection (the subject of the experiments) was raging. Upon either hypothesis, that of selection or of immunization, the mice which had survived varying periods in the testing herd would be expected to compare favourably with the untested immigrants to the experimental herd in respect of longevity.

TABLE I
Cage B. All A. Mice and all C. Mice. (Specific deaths only.)

	Length of Exposure in Cage A. (Days).	Number in Group.	Length of Life in Cage B. Limited to 60 Days.
C. mice ...	0	887	22.37 ± 0.36
	10	173	21.34 ± 1.10
A. mice	20	163	25.50 ± 1.13
	30	123	32.55 ± 1.28
	40 & 45	90	33.08 ± 1.52
	50, 55 & 60	73	37.39 ± 1.69
	65, 70, 75, 81, 90 & 165	58	30.29 ± 1.90

∴ Difference between A.'s and C.'s = 6.07 ± 0.66 .

We found that the superiority increased with length of survivorship in the testing herd not indefinitely but up to a comparatively early maximum; mice which had survived forty or more days did not succeed better than mice which had only survived thirty days in the testing herd. We also found that mice which had been exposed in the testing herd during a period of comparatively low mortality had an advantage over the untested immigrants, less indeed than mice which had lived through more strenuous times in the testing herd, but still quite substantial. Hence, on a general balance of the evidence, we concluded that the factor of active immunization was probably more important than that of selection of the fittest in conferring an advantage.

TABLE II

A. Mice whose time of exposure in cage A. was at an average death-rate of <0.00755 and C. Mice.

	Length of Exposure in Cage A. (Days).	Number in Group.	Length of Life in Cage B. Limited to 60 Days.
All C. mice	0	887	22.4 ± 0.36
C. mice corresponding to these A.'s.	0	493	20.9 ± 0.49
	10	59	23.3 ± 1.60
	20	38	23.8 ± 1.99
	30	39	25.4 ± 1.97
	40	30	28.6 ± 2.24
A. mice	50	9	34.6 ± 4.10
	60	10	33.7 ± 3.89
	65	9	22.4 ± 4.10
	70	8	31.5 ± 4.35
	75	10	14.9 ± 3.89

∴ Difference between these A.'s and all C.'s = 2.71 ± 0.92 days.

∴ Difference between these A.'s and contemporary C.'s = 4.2 ± 0.97 .

I do not, of course, mean to suggest that we attach little importance to innate variations of natural resistance and to the elimination by death of the less resistant, but merely that, in our judgement, the chance factor (as it can be loosely termed) of varying dosage of infection and the actual biological change effected in all or in a large majority of the exposed to risk by previous sublethal infections, together constitute at least as important a factor of the general situation.

EFFECT OF PRE-IMMUNIZATION ON ANIMALS EXPOSED TO RISK

With respect to the effect of pre-immunization on animals exposed to risk—evidently a matter of great practical and theoretical interest—the following table is instructive.

TABLE III.
Probability of Surviving Five Days.
Specific Deaths.

Cage Age in Days.	E, F, G.	Controls.	Difference.	Column 2 Column 3.	Graduation of Col. 5.
0	0.9968	0.9925	0.0043	1.004	1.001
5	0.9946	0.9715	0.0231	1.024	1.009
10	0.9679	0.9151	0.0528	1.058	1.039
15	0.9351	0.8291	0.1060	1.128	1.113
20	0.8261	0.6909	0.1352	1.196	1.217
25	0.7164	0.5691	0.1473	1.259	1.274
30	0.7053	0.5875	0.1178	1.201	1.229
35	0.8064	0.6813	0.1191	1.175	1.126
40	0.7619	0.7270	0.0349	1.048	1.046
45	0.8121	0.6984	0.1137	1.163	1.011
50	0.8295	0.8210	0.0085	1.010	1.002
55	0.8786	0.8593	0.0196	1.023	1.000

This herd was exposed to aertryckal infection and the E, F, G mice were effectively immunized before admission. It will be seen that their advantage in respect of average chance of surviving during the next five days' exposure increases to a maximum about the twenty-fifth day of cage life and that the advantage increases to, and declines from, this maximum in an approximately symmetrical way. This demonstrates well the very great advantage of pre-immunization when the period of exposure to risk is limited. For instance, by the thirtieth day only about 30 per cent. of controls will survive, of effectively pre-immunized mice more than 50 per cent.—an immense advantage. But the mice which survived to the thirtieth day are much less sharply differentiated and those which survived to the fortieth hardly at all. At that age one of the control groups had a limited expectation of life intermediate between the best and the worst of the three pre-immunized groups.

COMMENTARY

The ultimate approximation of the rates of mortality of the different groups might be explained in terms of many hypotheses. I suggest that the simplest is on the following lines. It is unlikely that any artificially induced immunity would ever be more effective than that conferred in the ordinary course of herd life upon the survivors of continuous exposure to infection. The advantage derived from pre-immunization—a very substantial one—is to bring the survivors at a certain date into as good a position as the surviving controls without having made them pay the price in high mortality which occurred in the controls. Divide a set of ordinarily intelligent persons into two batches, leave one batch to their own devices, provide the other with good teachers of some subject, and examine both batches at regular intervals, admitting no candidate to a subsequent examination who has been ploughed in the one before. We should find the proportion of ploughs in the earlier examinations much higher among the self taught, but ultimately we should expect the percentages to approximate and the quality of the ultimate survivors of both groups to be much the same. That in our case the ultimate survivors of both groups still experience a heavy mortality is, I suggest, due to the impossibility, in infections of this type, of raising the standard of resistance above some critical value. Neither by pre-immunization nor by natural immunization can we produce mice which are impervious to the continued bombardment of infection which the conditions of herd life impose.

SUMMARY

The further discussion of this matter would take me beyond the boundaries of statistical analysis, and I will conclude by summarizing the points which seem to me well established:—

1 In herds of mice exposed to heavy risk of infection of the type we have investigated, the regular addition of

healthy animals, and careful exclusion of new infection, will lead to the perpetuation of the disease through many generations. In small herds the infection may cease, in large herds it will probably be perpetuated indefinitely.

2 We can find no conclusive evidence that environmental, non-specific factors, modify in any significant way the secular course of epidemicity in our herds.

3 Pre-immunization will greatly lower mortality during the early herd-life of the pre-immunized animals. Ultimately the rates of mortality of pre-immunized and naturally immunized animals approximate to a level much above zero. In these infections a solid immunity—namely, an approximation of the specific mortality of the herd to zero—cannot be attained by any method which has so far been tested.

ADDENDUM

Since this opening paper was written we have gained enough experience to authorize us to suggest that in virus infections herd immunity develops on lines other than those illustrated in the bacterial infections we have studied. The kindness of Miss J. E. Marchal, of the National Institute of Medical Research, has enabled us to study in herds the virus disease, infections *Ectromelia*, which she first described in 1930 (*Journ. Path. and Bact.*, 33 ii., 1930, 713.) Miss Marchal discovered this infection in a stock of mice; it is clinically characterized by an oedematous swelling of a foot, followed by gangrene and separation, but often goes on to generalized illness and death. Miss Marchal proved that the essential *materies morbi* was a virus, and that animals which had passed successfully through an attack were very resistant to the injection of virus-containing substance. We have, down to June 30th, 1931, had two herds infected with *Ectromelia* under observation respectively for 224 days and 166 days. In the former 672 mice and in the latter 495 mice have been at risk, and the aggregate mouse-days of exposure were 25,168 and 16,374 respectively.

So far as experience during the early days of cage life is concerned, these heavily infected communities differed in no material way from the similarly treated herds wherein either *Past. muriseptica* or *Bact. aertrycke* was the *materies morbi*. But when the rate of mortality began to decline the fall continued, passed below the asymptotal line which characterized the bacterial infections, and ultimately reached a level differing in no important way from that of the rate of mortality of uncontaminated herds. The table (Table IV) compares the limited expectations of life of *Ectromelia* herds, a *P. muriseptica* herd

(P_3), and of a herd not exposed to any infection. The latter, of course, enjoy an expectation which, even at entry, falls but little short of the theoretical 60 (their slight inferiority to mice kept under conditions as nearly ideal as can be realized in captivity is attributable to the fact that, in a large herd, battle, murder and sudden deaths are of more vital statistical importance than in small groups). The *Ectromelia*—and the bacterially-infected herds have expectations of life at entrance less than half the theoretical value, and, as we have already seen, the bacterially infected do not, at any age, attain a value much above 50 per cent. of the ideal. By the 50th day of herd life the survivors of the virus infection are almost on a par with the normal mice, and the evidence suggests that this advantage will not be lost, that the survivors in these highly infected herds admitting unsalted immigrants are as little endangered by their environment as the parents of children with measles in an urban community.

SUICIDE FROM THE SOCIOLOGICAL ASPECT*

BY

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Suicide, from whatever aspect it is approached, is undeniably an important subject. It is one which for many years has interested me; and, for a number of years, it has been my habit to collect newspaper cuttings and other records of suicides in the hope that opportunity may present itself to gather together the special points which have occurred to me in the course of their perusal. My collection is quite a haphazard and miscellaneous one, and is much too large to permit analysis of it at short notice for the purpose of this discussion. Without any such analysis, certain points, however, have forced themselves on my notice, of which two or three may be appropriate to this discussion.

SUICIDE A MEDICAL PROBLEM

For instance, the almost complete failure to realize the existence of medical problems beneath every case of suicide, coupled with the fact that most of these problems require for their right handling an adequate knowledge of mental disorders. As a consequence, is that contentment which exists with the present often far from effective procedure; and, with respect to inquests in cases of suicide and to charges of attempted suicide, the further failure to see the place they occupy in problems of Mental Health and the peculiarly valuable opportunity they offer for promoting Preventive Medicine. With rare exceptions, those, in whose hands lie inquests and charges of attempted suicide, not only treat these occurrences as *prima facie* crimes, as is their duty according to present law in England and Wales, but they proceed to treat the parties concerned entirely upon socio-legal lines, and almost invariably ignore or mishandle the medical or psychological aspect. It is not my wish to cast any aspersion or adverse criticism on these men and women either individually or collectively. Quite the reverse. Over and above professional attainments (to praise which on such an occasion as the present would be an impertinence), coroners and magistrates, for these it is who are mostly concerned, we know to be

TABLE IV.
EXPECTATION OF LIFE LIMITED TO 60 DAYS.

Cageage in days	<i>Ectromelia</i> 1 (18.11.30-30.6.31)	<i>Ectromelia</i> 2 (16.1.31-30.6.31)	P_3 (6.3.21-30.4.23)	Normal mice (4.10.29-27.5.30)
0	26.86	28.37	22.49	56.79
1	26.13	27.66	21.82	56.86
2	25.39	26.90	21.31	56.76
3	24.61	26.13	21.05	57.02
4	23.92	25.42	21.28	57.10
5	23.14	24.70	21.48	57.37
6	22.39	23.98	21.86	57.29
7	21.85	23.57	22.32	57.21
8	21.66	23.38	22.57	57.12
9	22.33	23.70	23.00	57.03
10	22.69	24.04	23.48	57.12
11	23.35	24.28	23.55	57.03
12	24.47	25.22	23.76	57.30
13	25.35	26.30	24.04	57.22
14	26.51	26.66	24.54	57.14
15	27.86	27.58	24.96	57.05
20	36.48	34.62	29.62	56.79
25	42.98	42.53	33.12	56.72
30	47.07	44.53	34.41	56.69
35	51.13	48.46	34.74	57.65
40	51.12	48.81	33.81	58.30
45	54.17	50.92	32.63	58.42
50	54.24	53.28	32.23	58.37
55	53.42	54.99	31.70	58.52
60	55.14	55.74	32.06	58.47
65	56.64	56.64	32.37	58.44
70	56.66	56.06	32.96	58.62

* Read in opening a discussion in the Section of Neurology and Psychiatry, at the Annual Meeting of the British Medical Association, Eastbourne, 1931.