# Section of Epidemiology and State Medicine.

President—Dr. JOHN C. MCVAIL.

## Experimental Epidemiology : Some General Considerations.

By M. GREENWOOD and W. W. C. TOPLEY.

SIX years ago Dr. F. G. Crookshank contributed an interesting paper to the proceedings of this Section, entitled "First Principles: and Epidemiology.[1]" Dr. Crookshank was not very favourably impressed by the general level of epidemiology and remarked with truth that "few indeed of those who sit in offices and peruse records, tables and other statistical paraphernalia are gifted with the scientific imagination that enables them to form a picture of *all* that is passing beneath the eyes of others who are at work in general practice, in the dispensaries and in the casualty departments of our vast metropolis." He also said that "field work is required now more than ever, it is true; but it is also no less true than when Darwin said so, that, without hypothesis, there is no useful observation." We unreservedly accept these statements, the truth of which our several avocations have given many opportunities to realize. The statistician is the last person who needs to be told that statistics hardly ever tell one the whole truth and never tell one anything worth saying, unless one knows what question to ask. The bacteriologist does not want to be reminded how unilluminating can be the results of field work carried out with unimpeachable technical skill and without imagination.

We are not sure that we agree with Dr. Crookshank either in his explicit opinion that the "free discussion of fundamental and general principles will lead to better and more fruitful work, by those who have chosen certain lines of research for their own," or in his implication that an attentive study of, say, Ballonius, would help us to mend our ways. But we have certainly no pretension to lay down the epidemiological law to others. We hold merely that why *we*, and people like ourselves, do not understand the epidemiology of any disease (if for brevity we may still be permitted to use that unphilosophical word) is because we simply do not know enough to understand the answers which "Nature" is giving every day to our rather unintelligent questions. We are in fact, like Macaulay's imaginary Frenchman who, knowing just English enough to read *The Spectator* (with a dictionary), should attempt to defend the authenticity of Ireland's *Vortigern and Rowena* against Malone. That Frenchman would not have done better by embarking still more deeply upon textual criticism; he should return to his grammar and dictionary. It has seemed to us that before we could hope to understand "epidemic constitutions" and suchlike high matters, before we could even explain how scarlet fever epidemics arise—a matter still, it would seem, just a little uncertain—it might be well to practise on epidemiological events more within our control or, shall we say, less wholly beyond our control. It was that motive which led us to enter into a scientific partnership some years ago. The articles of association were these. That we should each bring into the common stock such special knowledge of particular techniques as we had individually acquired, but that the business of the firm should really be a joint one, that neither partner was at liberty to disclaim not mere formal but real responsibility for the work of the other.

We have worked together on this basis for some time and the object of this paper

[1] *Proceedings*, 1920, xiii (Sect. Epid.) pp. 159-184.

is to enlist the sympathy of those who are concerned with larger problems of epidemiology. We sail some of our model yachts in the children's pond and invite real sailors to tell us whether their motions have any instructive resemblance to those of real ships. Simple as are our conditions in comparison with those of real life, for we are wholly concerned with populations subjected to a quarantine of much greater rigour than the most autocratic sanitary authority has ever been able to enforce and exposed to infections qualitatively restricted, they are not absolutely simple and have given rise to various complex problems of interpretation. We shall, therefore, confine ourselves to the discussion of only a few problems, taking results which, as we think, have the most immediate relevance to the problems with which practical epidemiologists have to deal.

We take first the question of persistence. We think it is correct to say that just as the old prescription of flight into clean air was motived by, or at least rationalized into, a doctrine that epidemic illness was "caused" by a noxious condition of the "atmosphere," the modern prescription of isolation hospitals made its appeal to the belief that the best way to stop infectious epidemics was to shut up affected persons. The shutting up of persons suffering from, for instance, scarlet fever, has been going on for two generations. In London only a very small proportion of the ostensibly affected escape segregation. Neither statistics, however, nor general medical opinion, give the least indication that scarlet fever is at all less prevalent than it ever was. Why this disappointing result should be found is a question different epidemiologists have answered in different ways. One answer is that scarlet fever is now so mild that many more cases are missed and there is more uncontrolled infection. The mildness of present day scarlet fever can, however, hardly be attributed to isolation, since even in the short period of 250 years the malignancy of scarlet fever has undergone at least three revolutions. A century ago it was very mild, fifty years ago it was very malignant.

We must of course keep these two properties, malignancy and prevalence, distinct in our minds; for the moment let us consider prevalence. In the course of an official inquiry now almost completed, one of us and his official colleagues have had to examine the whole of the evidence respecting the prevalence of scarlet fever in this country, to attempt to answer the question: Does hospital isolation have any effect upon the *incidence* of scarlet fever? Officially there are really only two ways of trying to answer that question. The first is the directly statistical. We can use the figures of isolation rates, notification rates, and such other indices—say overcrowding rates—as we may think possibly relevant, and measure the relation between isolation and notification rates by some technical method of statistics. The second method, the indirectly statistical method, is to ask a number of persons with administrative experience of scarlet fever whether they think isolation has affected incidence. Both methods have been employed and have led to the same conclusion. All applications of the calculus of correlations have wholly failed to bring out any connexion whatever between the incidence rate of scarlet fever and the extent of isolation. The variables are independent, for all practical purposes. The other method gave this result: Of 726 medical officers of health only a few more than half (369), believed that isolation favourably affected incidence. The interpretation of these indirect statistics is, of course, affected by psychological conditions. But even medical officers of health are human. If in a plébiscite of cobblers only a bare majority could be obtained to favour the proposition that boots keep the feet dry, one would surely have more than a doubt as to the economy of re-soling. It would be interesting to apply these two methods to a still more drastic case, that of the diseases of animals other than man. It is true that in some parts of the country the isolation of scarlet fever patients is so complete that few escape removal. In London in 1923, 13 Metropolitan boroughs isolated 95 per cent. or more of the notified cases. But segregation in a comfortable hospital for a few weeks is a much

less radical application of the principle than the immediate slaughter of affected members of the community. Our veterinary colleagues used to apply this principle in all its rigour to swine fever, and still apply it to foot-and-mouth disease. Neither disease seems to have been eliminated, but the data open to us are too scanty to merit discussion. We can certainly say that foot-and-mouth disease behaves precisely as we should have expected it to behave by analogy with our experiment—shortly to be described—if certain conditions are fulfilled, but we are not in a position to say that those conditions *are* fulfilled. Returning, then, to the case of scarlet fever and assuming that segregation has in fact failed to diminish the prevalence of the disease, we must seek an explanation. That which suggests itself at once is the phenomenon invoked by several epidemiologists and utilized with particular skill by Sir William Hamer to account for the periodicity of measles, viz., the introduction into the community of susceptible individuals. Is it possible that we can maintain an infectious disease indefinitely by adding to a community unaffected individuals? To this question we have sought a decisive answer. The experimental procedure has been this: We started with an acute infectious disease of bacterial origin, a pasteurellosis, which had occurred spontaneously among a batch of purchased mice, but which has never spontaneously occurred in normal stock. The original herd consisted of animals some of or all of which had survived exposure to the infection. The herd was housed under conditions which would make the mouth of the most autocratic and scientific medical officer of health water. There was no question of mere spraying the walls and whitewashing the ceilings after the removal of a case. Every day, whether a case of disease occurred or not, the whole population was transferred to fresh sterilized habitations and all their furniture was sterilized. There were no fomites, and the housing conditions were ideal. Certainly the gregarious and combative habits of the mouse did lead to overcrowding—the practice of living in the kitchen and having a museum is carried to excess by mice—but the potential floor space was on a princely scale.

Immigrants to the community were supervised far more jealously than on Ellis Island. They were housed in cages similar to those of the herd, in groups of five to eight for three weeks. If any died during that time and autopsy revealed an infection known to cause epidemic disease, all the candidates for immigration were at once killed. If a death occurred for which no cause could be found, the quarantine period was extended by 14 days, and if a second death occurred the survivors were sacrificed. This process, so far as pasteurella was concerned, was completely successful, but *Bacillus aertrycke* and *Bacillus gaertner* sometimes got through the barrage and complicated the experiment.

The herd was recruited only by immigration; any young not devoured by the adults were removed.

The experiment to which we wish to direct attention first has been going on for nearly five years, which is, taking into consideration the relative lengths of life of mice and men, equivalent to much more than a century of human history. The Pilgrim Fathers of the community were 26 mice, survivors of a previous experiment, who founded the new colony on March 5, 1921. For a little more than two years until April 30, 1923, three approved immigrants were admitted daily. Since then only one immigrant has been admitted daily.

The history of this little community, wholly exempt from *res angusta domi* in any sense of the phrase, well fed, well housed, with nothing to do but eat, fight, make love and sleep, shielded from contamination by super-medical officers of health, and most efficient birth control, is interesting in many ways. Let us first consider it from the standpoint of the non-medical historian, i.e., as a story of population growth.

Soon after the colony was founded there were troubles, such as, the historian would say, attend the birth of most States, and the population increased very little for five months or, say, twelve human years. Then the community entered upon

a golden age, the mortality declined, and the population steadily increased until by October 8 it consisted of 182 happy citizens, seven times its original strength, or, approximately, it had increased as much as the population of England and Wales increased between 1700 and 1911, and, like that increase, the upward movement was an affair of the last part of the time (in England and Wales population hardly increased at all between the time of Elizabeth and the last thirty years of the eighteenth century). But this happy state of affairs did not last. From October 8 the population began to decline inexorably; by March 4, 1922, there were only fifty left. Worse was to come; the numbers fell to scarcely more than the original twenty-six, but then there was a turn for the better, and on May 1, 1923, fifty-eight, a little more than twice the original strength, were alive. This first epoch of mouse history covered almost two years and two months. If we take a mouse year as equivalent to thirty human years (the average life of a mouse seems to be about two years), this corresponds to a history of sixty-five years. The average population was 63·5, and the mean immigration rate is therefore 4·72 per cent. per diem, or, in human ratios, per mensem, i.e., 56·6 per cent. per annum. This doubled the population in sixty-five years.

On May 1 a new immigration law came into force. Only one mouse was allowed to enter. When this law came into force the community was in the throes of an epidemic, but, as the historian would say, the firm measures taken had their effect, and, in spite of the reduced immigration—in consequence of it, as the legislators might have affirmed—the population increased and approached seventy by July, 1923. Fresh civil disturbances arose, however, and the population again declined and even dwindled to twenty-two, less than the original number; but matters improved, population increased slowly but surely, and on March 14, 1925, reached eighty-one. But the troubles were not over; from that point to the middle of June the community dwindled and actually looked extinction in the face; fell well below twenty. But again there was a recovery. By the beginning of July the census showed forty inhabitants, and in the last months of 1925 there was little fluctuation. On the last day of the year there were forty-two. Looked at from the historical point of view we can see that the legislation of May 1, 1923, was a mistake. In the seventy-five human years since then the population has fallen from fifty-eight to forty-two, and has for several years exhibited that stagnancy which, we have been assured, is so dangerous.

That is, in outline, the civil history of this State.

We shall now consider its medical history. During the first mouse-year pasteurellosis was not only the reigning but almost the only fatal disease, but at the end of the year *Bacillus aertrycke* (Mutton) got through our barrage (after the mischief was done it was discovered that a considerable stock of supposedly normal mice carried both *Bacillus aertrycke* and *Bacillus gaertner*), and this new disease has never been eliminated. It was, so far as the community were concerned, literally a new disease and unquestionably imported by immigrants. This intruder for a time secured epidemic control and the epidemic constitution changed from Pasteurian to Aertryckian. There were, in fact, between June 27, 1924 and January 5, 1925, no deaths at all chargeable to pasteurellosis. As in human terms, that is about fifteen years, immigration officers might reasonably have congratulated themselves that *at last* pasteurellosis was stamped out; but on January 5, 1925, a dead mouse exhibited the stigmata of both *Pasteurella* and *Bacillus aertrycke* infection. As, however, the Aertryckian Epidemic Constitution was then reigning in a vigorous way, no serious epidemiologist would have had any difficulty in explaining away the finding. But the Aertryckian constitution waned, and on March 12, 1925, a fresh series of pasteurellar deaths began to occur, and continued for just under three mouse months, or seven and a half human years. Aertrycke resumed control then, and since June there has only been one pasteurellar death (on December 14, 1925).

It is interesting to speculate, in the manner of Mr. H. G. Wells, alas, *longo intervallo*, as to how this series of events might have been interpreted by the mice themselves. There would surely have been a party favouring the tightening up of immigration control, indignant at the entrance of *Bacillus aertrycke*, enthusiastic supporters of the law of May 1, 1923, and almost offensively triumphant over the obvious consequences of firm public health administration during the next ten years. Probably they would have died before being proved false prophets. But, even if they survived they would not have lost prestige; they could have argued that the control of immigration was still incomplete.

There would also have been a few erudite mice; one conceives their transports of contemptuous amusement when the administrators of 1923 proclaimed the Aertryckian infection a new disease. "Have you," they would ask, "paid attention to the events of forty years ago, the strange sicknesses—it is very unphilosophical to talk about diseases—which were prevalent in the time of our ancestors, all far wiser mice than we; there is nothing *new* about these prevalences. Cease to chatter idly about novelty. When you fully comprehended the nature of the vast genii who at roughly periodic intervals transport us, in a manner still obscure, from one habitation to another, when you fully and exactly grasp the whole cosmos, embracing us mice, the genii themselves, and the larger genii which no doubt control *them*, you will have a right to call yourselves epidemiologists, and be sure that whatever you *do* discover will be no more than a tedious amplification of what our incomparable ancestors believed, as we—when you *have* made the discovery—shall not fail to mention." Lastly, there would have been a still smaller party of algebraical mice, sedulously analysing the records of mortality, who would not even have provoked contradiction, for their results would be unintelligible to all other mice, and they themselves mainly interested in criticizing each other's methods.

We think this experiment has taught us a great deal. In the first place it has, in our opinion, brought the doctrine of Epidemic Constitutions within the compass of rational inquiry. The successive waves of epidemic sickness have occurred in such a manner and at such time intervals (taking account of the differences of life-span of mice and men) as, in human medical history, gave rise to the doctrine of Epidemic Constitutions. In comparison with the real epidemiologist we have indeed had one disadvantage, viz., that our *clinical* observations were restricted to the fact of death; we knew nothing of the patients' symptoms. But we have had a great many advantages. The social and economic milieu has not changed, the rate of increase has been strictly controlled and, excepting the victims of cannibalism, all deaths have have been certified with pathological accuracy.

The epidemic constitutions of our mice populations are not, we submit, directly or indirectly due to any occult and inexplicable change in the very bowels of the earth, as Sydenham would have it, nor to any super-meteorological phenomena, whether variations of terrestrial magnetism or any other of the high cosmic phenomena which some modern *Gelehrte* have advised us to study. They are certainly due to something happening in the population which we may not have wit enough nor live long enough to unmask, but which assuredly will be discovered by a suitable application of the statistico-experimental method. Of course *comparaison n'est pas raison.* Perhaps our epidemic constitutions are only pseudo-constitutions, not to be confused with the real Simon Pure. But since we *can* thus study the waxing and waning of epidemics associated with different micro-organisms under experimental conditions, which in absolute time have a rhythm on a different scale from that of human epidemic successions; since both rhythms cannot keep step with the high cosmic phenomena of Sydenham and his admirers, we shall adopt a Philistine pragmatism and jettison any interpretation of Epidemic Constitutions which cannot be subjected to experimental verification. We shall not ask to see it "on a plate" but we shall certainly ask to see it in a cage of mice.

We now return to the question whether this experiment throws any light upon the value of removing infective individuals from a community into which non-immunes are allowed to enter. We think it creates a presumption that such removal is, *from the point of view of the community*, largely futile.

It will at once be objected that we have never removed a single infected animal until he died, so that we have no parallel whatever with the practice of a human community isolating frank cases of infectious disease. But in this experiment there was a period of six months, equivalent to fifteen years, without a single death from *Pasteurella* infection, yet the infection revived without re-importation. It would, indeed, be remarkable isolation of, say, scarlet fever, which could place a human community for fifteen years in so favourable a position from the point of view of reduction of infective material. Yet the disease was not conquered. This is not a solitary instance. We have two other experimental colonies, each started by twenty pilgrim (and infective) fathers, and each continued for nearly two real years, say sixty human years. They were both inaugurated on February 14, 1924 ; in one (we call it Experiment 5), one mouse had been added every second day, the other (Experiment 6) has received an immigrant every third day. In neither population has the purity of the experiment been troubled by the incursion of any other infection. The histories of the two colonies are these. Experiment 5 began with four small waves of mortality and then enjoyed a quiet interval of two months (say five human years) during which the population reached forty, double its original strength. Then another epidemic began and in September—October, 1924, the population fell below its original strength. It recovered to nearly thirty in the early spring of 1925, but an epidemic in June brought it down to seven, when it began to increase, and in December, 1925, had reached 37. In the epidemic waves nearly all the deaths were definitely proved to be caused by pasteurellosis.

The history of Experiment 6 is more remarkable. As in the other communities there were increases of mortality after colonization, but no important movement until July, 1924 ; the colony passed through this crisis and in September had twenty-five members, five more than the original number. By January, 1925, this population had been reduced to 15 when it began to increase, reaching 30 on February 5, and remaining about that figure until March 19, 1925, when it again began to fall to twenty-one, but recovered to thirty by the second week of June, 1925, at which date a new epidemic began and reduced the colony to six. There was once more a recovery and in October, 1925, the population reached thirty-two, but fresh epidemics had reduced it by December 31 to less than ten.

A Malthusian mouse might use this history, the reaction of the colony to overpopulation by the positive checks of pestilence, to enforce the law that population always presses upon the limits of subsistence. The epidemiologically interesting point is this. Between July 20, 1924, and June 11, 1925, that is, over an absolute period of 325 days, almost twenty-eight human years, not a single death due to *Pasteurella* infection could be proved to have occurred. The last survivor of the July, 1924, epidemic of pasteurellosis died, having been a member of the colony 64 days, on May 26, 1925, 17 days before the new epidemic of pasteurellosis began (unfortunately he was one of those not able to be examined post mortem).

This experiment confirms the inference we drew from the long latent period in the main experiment.

It is, we think, fully established that a population wherein such an infection as pasteurellosis exists or has existed will probably never be rid of the disease again *if* it admits healthy immigrants. Merely excluding infective immigrants will never suffice to eliminate the disease.

The critic will at once retort that this in itself shows that our experiments throw no light upon at least one great problem of epidemic disease. Bubonic plague *has* died out in England and Wales. Whatever we may say about at least some of the

fourteenth century plague, however much of it may have been primary pneumonic, there is no doubt at all that the plague of the sixteenth and seventeenth centuries was ordinary bubonic disease. Therefore there must have been vast numbers of infected rats. Rats are constantly receiving new immigrants, *per vias naturales*. Why is not rat plague going strong all over England to this day? We cannot answer that question, and will not evade the difficulty by a reference to the partial replacement of the black rat by the brown rat, nor by throwing the onus of explanation upon mutations of the *materies morbi*, although both these factors may be concerned. We shall keep to a factor within our sphere of observation, the study of which seems to be important. This is the ratio of potential susceptibles to potential (or actual) sources of infection. Some of our best epidemiologists have explained the periodicity of, for instance, measles epidemics by the arrival at a critical value of the ratio of susceptibles to infectives. Sir William Hamer expressed this hypothesis in quantitative terms in his Milroy Lectures of 1906. Dr. Brownlee, while not accepting the explanation, for reasons which are important, recognizes that it covers at least some of the facts and that we can in this way explain some important epidemic phenomena. The study of the spread of infection within houses, which we recognize may perhaps not be strictly relevant, *suggests*—it does no more, for the exact data are scanty—that the increase in the proportion of susceptibles has a different effect in different diseases. All would agree that measles is much more infectious (we are not quite sure that all would agree on a precise *definition* of "infectious") than scarlet fever. It is at least quite certain that when susceptibles are exposed to frank cases, the proportion of the former going down with the disease is very much greater, at least—five times greater—in measles than in scarlet fever. Now, Dr. McClure's extensive Manchester data, covering more than 15,000 cases of scarlet fever, showed that as the proportion of susceptibles in a house increased the proportion attacked did not sensibly change. In houses with one initial case and one susceptible the proportion of susceptibles attacked was sensibly the same as in houses with one initial case and three susceptibles. In some very careful records of houses with an initial case of measles which one of us compiled from the admirable manuscript data of our lamented colleague, Dr. Reginald Dudfield, the proportion of attacked susceptibles decreased as the number of susceptibles per house increased. In our experimental work regular increase of the number of susceptible immigrants from one every third day to six every day increased, almost regularly, the *rate* of mortality and diminished the intervals between the epidemics. In the population of mice receiving six a day, it looked as if—unfortunately this experiment was ultimately spoilt by the intrusive *Bacillus aertrycke*—had it been possible to keep the experiment going on we should have smoothed out the waves and maintained a high and fairly steady death-rate. In other words, that we should have reached a point at which, epidemiologically, the supply was just equivalent to the demand. What would have happened had we increased the supply *beyond* that point would have been a very interesting matter. We hope to examine the question again. We have at least not reached an upper limit of mortality by the method of continuous addition, i.e., so far increasing the quota of regularly arriving susceptibles increases the rate of mortality. But when we proceeded on another tack and introduced into a community not small batches of regular immigrants but large parties at long intervals, the epidemic mortality was low.

We started here with twenty settlers mingled with eighty immigrants (it will be remembered that the settlers came from an infected stock) on February 14, 1924. Eighty more immigrants were added on March 19, fifty on May 3, fifty on June 11, and fifty on July 1. At the beginning the death-rate was rather high. The first and, until the middle of August (i.e., after immigration ceased), largest wave of epidemic sickness lasted about a month; from the end of this the rate of mortality remained very low until some six weeks after the admission of the last batch, when

the mortality began to increase and eventually reduced the population to two. As a *Bacillus aertrycke* infection developed just before the arrival of the last fifty immigrants, the experiment is neither clean enough nor was continued long enough to be very satisfactory, but some points emerge. Although after the admission of each batch of immigrants the death-rate began to rise at the end of a few days the increases were quite small, and the average pasteurellar death-rate was low although the mean population was large, the second largest in our series. A sudden and great increase of the ratio of susceptibles to potential infectors did not lead to a violent epidemic. The conclusion we draw from this is that to ensure a high epidemic rate it is not enough to have a large susceptible population at risk and, conversely, that the comparatively healthiness of our small colonies admitting few immigrants was not a mere consequence of their small numbers. Perhaps some will suggest that the analogy is with a fire; put a few coals on it regularly and it burns brightly, empty the coal scuttle into the grate and it goes out. But the analogy is very crude, and we think a good deal more work must be done. We do not know of any exact studies on the effects of school openings after the holidays distinguishing schools of different sizes; they might be suggestive.

At present, all we think we know is that not the number of the susceptibles at a given moment in proportion to the infected or any simple function of that ratio determines the moment of an epidemic. The old tag, *gutta cavat lapidem non vi sed sæpe cadendo*, seems to apply. We would sooner admit 1,000 susceptibles to a herd at once than ten a day for a hundred days if we desired to keep down the rate of infectious disease.

We now come to a matter our investigation of which has hardly passed beyond the preliminary stage, viz., why does an infectious disease come to a temporary end? There are, at least, four theories. One is that the susceptibles are exhausted another that an active immunity is established; a third that the "epidemic constitution" changes; and a fourth that the organism ceases to be infective.

So far as our little cosmos of mice is concerned, we have given reasons for holding that the doctrine of "epidemic constitutions" in Sydenham's sense can explain nothing, so we rule it out. Dr. Brownlee's intellectual child, the changing life cycle of the parasite, is a sturdy infant to whom we may ultimately offer chocolates, but at present we do not quite understand his language and are not sure that he wants our chocolates. The two other theories *seem* easier to test, although we have got but a little way towards testing them.

This is the way we have gone to work. We established two colonies rather more than a year ago. Colony A was designed as a sort of purgatory. *Pasteurella* was established in it and clean immigrants introduced (the precise numerical details will be given elsewhere, they are not material to the present brief discussion). Another, Colony B—whether analogous with heaven or hell is doubtful—was recruited from two sources, (*a*) from mice who had passed through the purgatorial flames of A, (*b*) from pathologically blameless immigrants in all respects comparable with the immigrants of our other experiments. The matter for study was the fate of the two classes in B. Down to the time of writing many more than a thousand mice have entered B, either from A, or from a state of innocence (we call the latter C mice), and there is not the least doubt that, on the average, A mice live a good deal longer under B conditions than C mice. Thus, if we take as a measure the proportion of immigrants to B who lived at least twenty-eight days in B, this was 23·3 per cent. for C mice, 26·7 per cent. for mice who had lived ten days in A, 36 per cent. for mice who had lived twenty days in A, and as much as 55·6 per cent. for mice who had been able to stand purgatory forty to forty-five days.

If we took as a measure the average number of days lived from entry to B to death, there was the same superiority of the A's with this difference, that there was a tendency—we cannot put it much higher—for the superiority to increase to a

maximum with increasing sojourn in A and then to fall off. Thus in one series of entrants to B on a particular day, the C's lived on the average 34·1 days; the A's, with 10 days' experience in A, 41·3 days; those with 20 days' 53·6; those with 30 days' 49·6; and those with 40 days' only 16·7. Now the mere superiority of the A's might be equally well explained by the exhaustion of susceptibles or by the acquirement of immunity. The A conditions may have killed off the most susceptible, so that only the fittest are exposed to B conditions, hence their superiority to the unweeded sample of C's. *Or* mice are born epidemiologically equal and those who went through A were actively immunized. We see no reason to believe that either explanation is the whole truth, but what we do want to know is, which factor is the more important? The point we made above, viz., that the superiority of the A's did not (in the matter of length of life) go on increasing with length of sojourn in A is clearly against the pure selection theory and in favour of the hypothesis of acquired immunity, but, having regard to small numbers and variability, is not decisive. An attempt to cut the knot failed. We argued that if we compared—not the average length of life of the C's, but—the average length of life of the best of the C's with the A's we might cut the knot. Thus, suppose of the A's in the batch entering A, whose survivors went to B, the total mortality were 20 per cent. in A. Let us compare the longevity of the 80 per cent. who survived to enter B—not with that of their companion batch of C's but—with the length of life of the 80 per cent. longest—lived C's in the batch. Now if such a comparison still gave an advantage to the A's, it would be a pretty clear proof that selection was not enough. But if it did not give the A's a superiority it would certainly not prove that only selection was at work, for the possibilities of active immunization are still present in B. Actually the average longevity of the A's was greater than that of the best C's so defined, 33·3 against 29·5 days, but in individual batches the best C's were longer lived than the A's as often as not. The test did not give an unequivocal answer.

Two other pieces of evidence, however, told in favour of immunization against selection. The first was that length of life in B was more highly correlated with *length* of exposure in A than with the *severity* of the *death-rate* during exposure in A. It was better to have survived a moderate time in A under mild conditions than a short time in A under severe conditions.

Also, when we separately studied the histories of A mice who had never been exposed to a high rate of mortality in A in conjunction with C mice, it was found that the advantage of the A mice increased to a maximum as exposure in A increased and then decreased, just as we should expect if immunization rather than selection were the prime factor.

The average length of life of the corresponding C's was 20·9 days, of A's with ten days' training, 23·3; with thirty days, 25·4; with fifty days, 34·6; and then a decreasing advantage. A's, with 71 days' exposure lived only 14·9 days in B.

Neither piece of evidence is decisive; this study is only beginning, but the balance is in favour of immunization rather than selection. We know of no human data giving the results of subsequent exposure to a common infection of groups of persons who have passed through, some a mild, others a severe, epidemic, others no epidemic at all. The data collected by the Ministry of Health in connexion with the great epidemics of influenza are the most nearly in point. From these it appears that there were five out of twelve instances where those who had influenza in the mild summer epidemic had a significantly lower attack rate in the winter phase, and only four instances where those attacked in the autumn had a significant advantage in the winter. In other words, passing successfully through the very severe autumn disease did not, on the average, confer more protection than passing through the mild summer disease. For obvious reasons this is a very loose analogy; as pointed out in the report, the problem of immunity against influenza is an excessively complicated one.

At this point we must break off the story of our experiments. Perhaps it will be said: "Your positive contribution to knowledge is very meagre. After years of labour, holocausts of mice, much arithmetic, much expenditure of money, you have only proved that in communities of mice a particular microbial disease will continue indefinitely if you introduce fresh susceptible individuals, and that the disease will wax and wane, being at times replaced by another microbial infection, in a fashion similar to what occurs in human experience. You have made it probable that the form of the secular curve of epidemicity is dependent upon the rate of addition of susceptibles and that an acquired immunity as well as selective immunization have a part in the advantage survivors of one epidemic enjoy when exposed to another. All these things any reasonable man might have inferred from human experience. We know that measles has been endemic-epidemic since the days of Edward III and mumps since the time of Hippocrates. We know that persons can be actively immunized against diphtheria and that some families and, indeed, some races are far more susceptible than others to zymotic disease. Was it really worth while to spend so much time and money in demonstrating these notorious facts?"

We shall not rely as, for forensic purposes, we might upon the retort that if the medical world does indeed know all these things, it certainly does not act upon the knowledge, but still proceeds, at great expense, to act on the belief that epidemic disease can be controlled by the temporary segregation of sick human beings or the slaughter of sick beasts. We shall not rely upon that retort, since the obvious fact that hardly anybody is a consistent Christian is not a logical proof that Christian ethics are unsound.

Our defence is based upon the principle that no problem can be solved until it has been clearly enunciated, and that the problem, or group of problems, covered by the word epidemiology has never yet been clearly enunciated.

> *Sed nil dulcius est, bene quam munita tenere*
> *edita doctrina sapientum templa serena,*
> *despicere unde queas alios passimque videre*
> *errare atque viam palantes quaerere vitae.*

The administrator, or public health official (termed by his critics an office epidemiologist), the students of medical history and statistics (termed by *their* critics arm-chair philosophers and "mathematicians"), have all realized the sweetness of this position and been led by self-esteem to imagine that they are in truth occupants of heights of serene wisdom from which they can survey impartially the phenomena of human epidemic disease. But, in fact, neither an established civil service post, first-hand acquaintance with the writings of Ballonius, nor even a working knowledge of the theory of multiple correlation, is an adequate safeguard against the weakness of human nature, conscious of the fact that those whom we see from the heights, "wandering all abroad and going astray in their search for the path of life," are human beings, whose passions we share and whose applause we covet. They return to our serene questionings a great variety of answers, and we generally catch the answer we wish to hear. But even in these humanitarian days the calamities of mice do not stir our feelings over-much; mice cannot assure us that we are energetic administrators, philosophical scholars, or skilled mathematicians. The problems that their lives and deaths afford we *can* formulate with a decent objectivity.

In the course of this work we have presented to ourselves, although we may not have the literary art to present to others, a far sharper picture of the march in time of an epidemic disease than the confused palimpsest of human experience has given us. We seem to begin to understand the mechanism of the epidemic movement and the nature of herd immunity, how it is established and how it is lost. We perhaps shall not live to know enough of the mechanism to turn it to a practical account, but we have faith that when experimental epidemiology, now an infant, is full grown, the occupants of the *templa serena* will see the struggling masses below less confusedly, having learned what to look at.

Sir LEONARD ROGERS exhibited a number of charts illustrating the influence of climate on the prevalence of small-pox in India.

*Discussion.*—Dr. A. BALFOUR said that, after listening to this learned and philosophical paper, he felt that, unless one belonged to the class of "erudite mice" or to that of the "algebraical mice," or possibly even to both, it was not easy to discuss it to advantage. He did not belong to either of these groups, and hence did not feel competent to comment on the paper, but he would like to put some questions. Dr. Greenwood's remarks on plague in this country had specially interested him, and he wondered if d'Herelle's bacteriophage had played any part in bringing the great epizoötic in this country to an end. Quite recently d'Herelle had isolated a lytic principle from the fæces of rats during a plague outbreak in China, had cultivated it, and even used it at Alexandria in the treatment of bubonic plague. He suggested that Dr. Greenwood and Professor Topley might look into this question of a bacteriophage in the case of these mice epidemics if they had not already done so. He recognized, however, that they probably had more than enough to engage their attention. The hypothesis that the bacteriophage might play a part in terminating epidemics had, of course, been advanced. He would like to know what was meant by a "normal mouse population." They had heard about the control colony of presumably healthy mice, but deaths did occur amongst these mice, and it would be of interest to hear about the causes or mortality, as these might prove disturbing factors during the epidemics of *Pasteurella*, *gaertner* and *aertrycke* infections. He hoped that some day Dr. Greenwood and Professor Topley would turn their attention to yellow fever, a disease which presented interesting problems, although, of course, an insect intermediary had to be considered, and it introduced a complication to some extent.

Yellow fever was at one time endemic in St. Thomas, one of the West Indian islands, but it gradually vanished without any active steps being taken to hasten its disappearance. The island, at one time prosperous, had declined in importance, and, as a result, the influx of non-immunes diminished. The inhabitants had probably acquired a permanent immunity, and the number of non-immunes born in the island was not sufficient to keep the disease going. Such, at least, was the view held, and a useful comparison might be instituted between such an occurrence and the experimental work on mice. Of course yellow fever could not be transmitted to mice, but an examination of the historical and statistical data would be interesting and perhaps valuable. Again, take the large island of San Domingo. There had been no cases of yellow fever there since the early nineties of last century. Yet, before that time, the disease was present, and it had disappeared even though the island was in close touch with Cuba and other places when yellow fever was prevalent in them. No efforts have been made to combat the *Stegomyia* or to prevent the disease in any way. It died out spontaneously; why, no one knew. A consideration of this kind led him to think that possibly unknown factors might be present of which, at present, we knew nothing.

Dr. J. A. GLOVER compared the *Pasteurella* infection of Professor Topley's mouse population with the history of the meningococcus infection of the Guards Depot at Caterham, and he showed a graph of two of the four epidemic waves of carrier and case epidemics which had occurred there during the war. The Depot, with its large batch of additions of susceptibles, was most akin to No. 7 of Professor Topley's experimental series, and the Caterham graph (which, although it covered more than two years of human experience, was only equivalent to five weeks of Professor Topley's curve) showed distinct resemblances to some periods of that curve. By another diagram, in which years were superimposed, Dr. Glover showed that in the human community with meningococcus infection, environmental conditions, particularly overcrowding, were of greater importance than the cosmic influences of season and weather, highly important though the latter were.

Another point of resemblance to one of Professor Topley's experiments in which mice that had been previously exposed to infection were mixed with unexposed mice in a new community, was the fact that although the trained soldiers and the newly entrant recruits shared equally in the "carrier epidemics," not a single trained soldier suffered from meningitis; all the patients in the "case epidemics" being recruits.

It was interesting to note that in the Caterham graph the first wave (1917) shown was almost entirely due to Type II meningococcus. "Spacing out" and other prophylactic measures almost completely purged the Depot of this infection, and the second wave (that of 1918) was entirely due to Type I meningococcus.

Dr. E. W. GOODALL said that all epidemiologists were agreed that the number of factors concerned in the rise, continuance and fall of epidemics were often so many and complicated that it was extremely difficult to assign to each its proper share. Dr. Greenwood and Dr. Topley, therefore, by a most laborious and painstaking set of experiments and calculations were taking some of the factors singly so as to be able to ascertain as far as possible what part it played. He was of the opinion that so far as the infection with which they had worked was concerned they had made a most valuable contribution to the study of epidemiological factors and especially towards that of the increase of a population by the addition from time to time of susceptible individuals. He would, however, raise the question whether one could fairly argue from this particular set of experiments in order to explain epidemics in human populations of such diseases as influenza, small-pox and measles. He understood from a perusal of these and other papers by the same authors that the infections they used, *Pasteurella muris* and *Bacillus gaertner*, were infections which were taken in by the alimentary tract, as in the case of enteric fever amongst human beings. From his experience of what happened in children's wards and from what he had read of what happened in small isolated human populations, he considered that it was very doubtful whether it would be possible to keep such a disease, as for instance measles, going for the length of time the writers of the paper had kept their infections going amongst the mice. There was every reason for believing that such infections as measles, small-pox and influenza were taken in through the respiratory and not the alimentary tract. Some of the conclusions reached by the authors he had himself arrived at from an experience of nearly forty years in the administration of wards full of children, and especially that there was no surer way of keeping an infectious disease going in a ward (say measles in a diphtheria ward) than by admitting fresh susceptibles to fill any vacancies that might occur. Again, some of the mice in the experiments survived one or more epidemics only to succumb in a later one; so one saw children pass unscathed through one or two exposures to such a disease as measles and yet catch the disease on the third. The continuation of an infectious disease in a community might also depend upon whether it was a disease in which carrier cases were at all common.

These experiments also bore on the question of the acquisition of immunity by sojourn in a place in which a certain infection was more or less continuously in evidence. Some of the mice in these and similar experiments certainly did not become immune; apparently others did. While there was evidence that in human populations immunity to certain infections could be acquired in these circumstances—for instance to diphtheria, scarlet fever and enteric fever—there was none that he knew of, that immunity could be so acquired to such diseases as measles and small-pox. Here again it was possibly a question of whether the disease was or was not one in which the carrier condition could occur. He thought that the authors had rejected rather too lightly the variation of the infectivity of the micro-organism as a factor in the rise and fall of epidemics. The history of scarlet fever in this country in his opinion went to show that that variation was not an impossible factor, and more than one experimenter had shown that the passage of organisms through animals led to a diminution, certainly of its power of killing an animal and possibly of its infectivity.

The authors had touched on the question of the epidemic constitution. Their contention was right that that doctrine was brought within the compass of rational inquiry by such experiments as those they had undertaken. He was under the impression that that doctrine had ceased to be taught in this country soon after the middle of the last century, but it had recently been revived by very eminent epidemiologists and was, therefore, worthy of inquiry. We owed the term "*Epidemic* Constitution," that is constitution of the season, to Sydenham, for Hippocrates spoke only of the "Constitution." The Greek physician gave us a method of inquiry from which he himself obtained little if any results, because he had neither the time nor the material at his disposal. He evidently attached much importance to weather conditions as a cause of diseases, (as Sir Leonard Rogers had shown them that evening in respect of small-pox in India,) but he would have nothing to do with the mysterious. Sydenham, however, could not explain epidemics by weather or other natural conditions and, therefore, appealed to something outside or above them, and this he called the "Epidemic Constitution." But no clear definition of it could be found in his writings. It was for the modern revivalists with the accumulation of facts that they had at their disposal to explain the doctrine, but, in the speaker's opinion, they had invented only a super-constitution to that of Sydenham. Their attitude might be described in Fracastorius's words that those who invoked the occult had little trouble in ridding themselves of difficult problems; all they had to do was to look to the occult for the explanation.

The following observations were submitted in manuscript by Sir William Hamer and Dr. Forbes:—

Sir WILLIAM HAMER wrote: Of course those of us who love the rivers of Damascus do not like having to wash seven times in Jordan. But we rejoice, all the same, to find that the first lesson from the "uniform environment" (freed from human frailty and all cosmic influences) is that accumulation of susceptibles *does* (in part) determine periodicity, whatever the periodogram may say. An old friend of mine, who "knows his measles," notes that "this pasteurellosis is just measles over again!" And, as he says, "the problems which (we gather) are now to be faced by the new science are identical with those the old epidemiologists have been hard at work on since the Stone Age." In speaking thus, he is no doubt trying to adapt his history to the new time-scale of mouse epidemiology. He and I are, however, so fascinated by the abstract of the paper that we mean to wash in Jordan, even to seventy times seven, if that will cure us of our leprosy.

All the same, we feel there is some excuse for the old epidemiologists. How could they all describe epidemic disease—"varium et mutabile semper"—in precisely identical terms? True, there are a few so-called "stationary fevers," but far more epidemics of "unstable type." The most striking fact about the influenzas of history is that they have again and again been hailed as "new diseases." On the other hand, the charge that the primitive epidemiologists did not, from the outset, take the precaution of securing "unchanging social and economic conditions" must be regarded as proven. It is to be regretted that they just said, as Margaret Fuller was wont to do, "I accept the universe," and, in fact, took the world as they found it. But what an extent of ground, what stretches of time and space, their investigations have covered! A Westminster Abbey guide used to arrest the attention of American tourists, standing before Southey's memorial in Poets' Corner, by describing Lodore as a "waterfall in Cumberland about the same height as Niagara but not quite so broad." So, the mouse epidemiology is as high, no doubt, as the human, but as yet it is wanting in breadth. One word in conclusion: the authors of the paper confess that their "well laid scheme of mice" has already, like the schemes of the primitive epidemiologists, been affected by a disturbing influence—a Gaertner infection has surreptitiously crept in. They say, "This produced effects comparable with the phenomena which, in human experience, the doctrine of epidemic constitutions has been invoked to explain." The appeal must be to Sydenham. Would he, when a full 150 years' exclusive study of one stationary fever (pasteurellosis) was, at length, agreeably diversified by the appearance of a "new disease," have straightway jumped to the conclusion that "epidemic constitution" was in question? Would he not, rather, have declared that "the brief life of a single mortal would be insufficient" for the complete study of the inter-relationship, if any, between the two diseases? Time alone will show, so I shall continue, as before, to read all the works of Dr. Greenwood and Dr. Topley, hoping for the best; but, at my age, despite the rapid time-scale of mouse epidemiology, I cannot hope to live to be enlightened on the point.

Dr. GRAHAM FORBES wrote: Although, in the words of the poet, "the best-laid schemes of mice and men gang aft agley," such was not always the case, to judge from the very interesting and remarkable record of the experimental work to which they had just listened. Thanks to the ingenuity and perseverance of men and the compulsory co-operation of mice, the joint "schemes" had resulted in a considerable measure of success achieved towards the elucidation of epidemiological problems, if not actually in the eclipse of the impenetrable halo surrounding those "blessed" but mystifying words, "epidemic constitutions."

The absence of Surgeon-Commander S. F. Dudley, R.N., among others, from the evening's discussion was very much to be regretted; his "Study in Epidemiology of Scarlet Fever and Diphtheria," published by the Medical Research Council in 1923, and probably familiar to the majority present, was a piece of work of considerable value. His observations on the spread of the two diseases in a resident community, like those of Dr. Glover on cerebro-spinal fever, formed, from the human epidemiological standpoint, as near an approach as was conceivable to the mouse experiments with *Pasteurella* and *aertrycke* infections just described.

Therefore there could be little doubt that Surgeon-Commander Dudley's contribution could not have failed to add to the value of their discussion. His deductions leant strongly to the influence of acquired epidemic immunity as a factor to be reckoned with in explaining the spread of scarlet fever and diphtheria, if not of other diseases. There was much to be said in favour of his views. Moreover, one could not but be impressed by the attractive and ingenious

theory he had put forward of the principle concerned in epidemics, termed "the velocity of infection," and described as the resultant of the velocity of the reception of infection and of the velocity with which the mechanism of immunity was capable of destroying infecting agents.

Dr. TOPLEY (in reply) said that, of the two diseases which Dr. Greenwood and he had studied, the *Bacillus aertrycke* infection was almost certainly acquired via the alimentary tract, but all the available evidence suggested that mouse-pasteurellosis was a respiratory infection, so that, as regards its portal of entry, it might be regarded as analogous to such human diseases as influenza. In *Bacillus aertrycke* infection it was certain, and in pasteurellosis probable, that the majority of those mice which had survived any long exposure to risk had not escaped infection but had resisted it, and that many of them were harbouring the causative organism in their tissues. Dr. Greenwood and he had not rejected the possibility that variations in the biological properties of the parasite might play an important part in the course of events. There was no doubt that such variations did, in fact, occur under artificial cultivation. The question whether or not such variation played a significant part in the sequence of events they had described remained to be answered by future experiments.

The observations which had been made on the spread of cerebro-spinal fever during the war afforded the most interesting analogies to certain of their experiments, and the resemblance between the course of events which Dr. Glover had described at Caterham and the results obtained in certain experiments on mouse-typhoid was particularly striking.

A few experiments had been carried out on the effect of administering a bacteriophage, active against *Bacillus aertrycke*, to mice among which mouse-typhoid was actively spreading. The results had been uniformly negative, although the infection had a close general resemblance to fowl-typhoid, in which d'Herelle had recorded strikingly successful results.

Although there was a certain resemblance between the gradual immunization which appeared to occur among the experimental herds of mice, and the immunization which occurred during the spread of diphtheria among a human population, it would seem that very different factors must be involved, since the immunity developed by the mice appeared to be relatively imperfect and transient. It was possible that this was in part due to the difference between antibacterial and antitoxic immunity.

The study of the natural history of particular diseases in island communities, such as Dr. Balfour had referred to, would, if the data were adequate, be of the greatest service in determining whether the phenomena observed in experimental epidemics gave a true representation of the course of events in natural epidemics of disease among man.