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BY

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The mathematical and biological theory of epidemics has hitherto been treated by few writers, but it is a priori a branch of the theory of chance, and the mathematics of the theory of chance once properly applied should afford a solution applicable to all epidemics. The ideas which underlie the theory of chance are, however, complex, and there are not many workers who have both the mastery of this theory and the necessary epidemiological knowledge to permit of its application. The results of a preliminary investigation into this subject I propose to lay before you to-night. It makes no claim to be more than a beginning, but as far as it goes it shows that the main laws which regulate epidemics are as simple as the law of gravitation, though the application of them to the diverse conditions which govern epidemics is often of considerable complexity. The chief difficulty arises from the fact that there is no means at present known of directly measuring the power of infectivity possessed by an organism. The value and variation of this power can only be discovered by making various assumptions, and testing the truth or error of these assumptions by the degree of correspondence which the results obtained on each assumption have with the actual facts. This is, of course, but the general method by which the theory of chance has been discovered, as when it is applied to games of chance or to coin-tossing where some hours of experiment settle at once whether theory and fact have any correspondence.

The epidemiological problem is twofold. In its one aspect it concerns the distribution of epidemic disease in space. That is to say, if an infectious disease be introduced into the midst of a uniformly populated district, its subsequent distribution necessarily follows some definite law. Practically a complete mathematical solution of this part of the problem has been given by Professor Pearson, and his result only requires modification to meet particular cases. It is purely an application of the theory of chance. The second part of the problem concerns the distribution of epidemics in time; that is, the manner in which the number of new cases varies from day to day, and it concerns the laws which regulate the ascent and descent of the epidemic curve. This is not a problem in pure chance; it involves a knowledge of the rate at which certain things vary. It must be obvious that one of three things causes an epidemic to die out. Firstly, the conclusion of an epidemic may be due to the exhaustion of susceptible persons among the population. In the second and third place, either a loss of infectivity on the part of the organism or of susceptibility on the part of the population is necessary. This part of the subject is biological and independent of the theory of chance, and will first be considered.

There are two ways in which the biological basis of epidemics may be ascertained: one is by observation of the mode of epidemic progress, either as it occurs in nature or in experiment; the other is by examination of the accumulated statistical information at our disposal. The latter at present lends itself much more easily to discussion. The fact which presents itself at once to our notice is the near symmetry of the form of the epidemic curve. If any typical epidemic of plague, as at present in India, or in former times—say that of 1665 in London—is examined, it is seen at once that as the disease increased, so it declined. That is even more fully seen in those directly infectious cases, such as small-pox and measles. The last large epidemic of small-pox in London in 1901-2 is a case in point. In fact, take any large solitary epidemic (by this phrase I mean an epidemic in which the level from which the disease rises is only a minute fraction of the epidemic height), and the symmetry of the course is an obvious and well-marked feature. The deduction from this phenomenon is direct and complete—namely, that the want of persons liable to infection is not the cause of the decay of the epidemic. On no law of infection which I have been able to devise would such a cause permit of epidemic symmetry. The fall must in

all such cases be much more rapid than the rise, though, on the contrary, when asymmetry is markedly present the opposite holds. We are therefore left to explain the cessation of the disease on the ground of loss of infectivity on the part of the organism, or of a decrease in susceptibility on the part of the population. In either case the form of the epidemic curve allows the rate of this loss to be more or less accurately measured. Dr. Farr already gave the solution as far back as 1868, and his results were somewhat extended in a paper to the Epidemiological Society in 1874 by Dr. G. H. Evans. The form in which, however, Dr. Farr gives his arithmetical law of the epidemic does not allow of the underlying cause directly appearing. It remains a law without a reason. A different form of analysis is necessary to discover this. But the result is not difficult to ascertain. If, as he says, the second difference of the logarithms of the successive ordinates of the epidemic curves is constant, then it directly follows that the loss of infectivity of the organism is approximately in the ratio given by a geometrical progression. That is, if the infectivity of the organism of the epidemic is m, and at the end of a unit of time mg when g is less than unity, at the end of a second unit of time it will be mg^2, at the end of the third mg^3, and so on. Dr. Farr seems to have chiefly considered the matter from the point of predicting the course of the epidemic, and there he is subject to special difficulties, for at best a law of this kind only expresses an average, and to make a prediction from the necessarily inexact figures obtainable at the beginning of an epidemic is somewhat futile. It may be taken, however, as certain that something approaching Dr. Farr's law represents the actual facts, and, with modifications to be mentioned presently, it can be made to describe the course of many epidemics with considerable accuracy.

It is very difficult to give evidence at all conclusive as to whether susceptibility or infectivity plays the greater part in determining the course of epidemics, but to my mind the state of the organism as regards its power of infecting is much the more important. The explanation which makes an epidemic end because the whole susceptible population has passed through an attack of the disease is obviously out of count, but a few facts even on this point will perhaps be of interest. In the winter of 1907-8 one of the largest measles epidemics in the history of Glasgow occurred. Public health authorities can at present do very little in the way of limiting the spread of measles, so that artificial measures had practically nothing

to do with the passing of the epidemic, yet it ceased exactly as epidemics are regularly seen to cease. So little, however, did the absence of susceptible persons account for the disappearance of the epidemic that even immediately after the disease had ceased we were admitting child after child to the hospital who had not passed through an attack of that disease. I have extracted from the histories of 263 children suffering from whooping-cough, admitted consecutively between June and September of last year, the details of their previous diseases. Of these, 137 are stated to have had measles at some previous date, but the remainder, numbering 126, to have not previously had an attack of that disease. These children were from the age of 1 year and 6 months up to the age of 9 years. Children under the former age were not counted, as they would have been below the age likely to have been infected during the time of the epidemic. Even at the high ages there were many children who had not had an attack of the disease. As regards the trustworthiness of these histories, I have usually found when dealing with cross-infection in wards that on the average they were fairly exact. This example of measles is as good as any. With regard to small-pox, it can hardly be said that out of the whole population of London in the year 1901-2 only 9,000 were susceptible to that disease. If this be the case, the fact seems to admit of only one interpretation, and that is that the infectivity of the organism is the chief factor in the course of an epidemic. It is easy to understand that a faculty acquired by an organism should be lost at a definite rate, as in its life-history the process of division completes itself every few minutes or hours. It is much more difficult to conceive that human or animal susceptibility should vary in such a manner that on December 1 the susceptibility to small-pox should possess exactly the same ratio to the susceptibility on January 1 as the latter possesses to that on February 1. The other alternative seems much the most probable.

At this stage it is perhaps well to illustrate theoretical and typical forms of epidemics. In the accompanying diagram I have drawn alongside in comparable scales four figures. In fig. A a diagram is given which would show the epidemic form if the disease died out simply from want of susceptible persons. It is markedly asymmetrical, the fall being much more sudden than the rise, which is in contradiction to common epidemic experience, as even when the epidemic is not symmetrical the decline is in general more prolonged than the rise. In fig. B is seen the form of the epidemic of small-pox in Boston, U.S.A.,

in the year 1721. This town at the beginning of the epidemic contained about 5,000 people not protected by a previous attack of small-pox, and of these 4,500 were attacked. This epidemic may thus be fairly considered as one in which the disease ceased because there was no susceptible material left, and though it does not accurately correspond to the previous diagram, yet it shows a considerable resemblance to it. This epidemic is, however, an almost unique example. In figure C

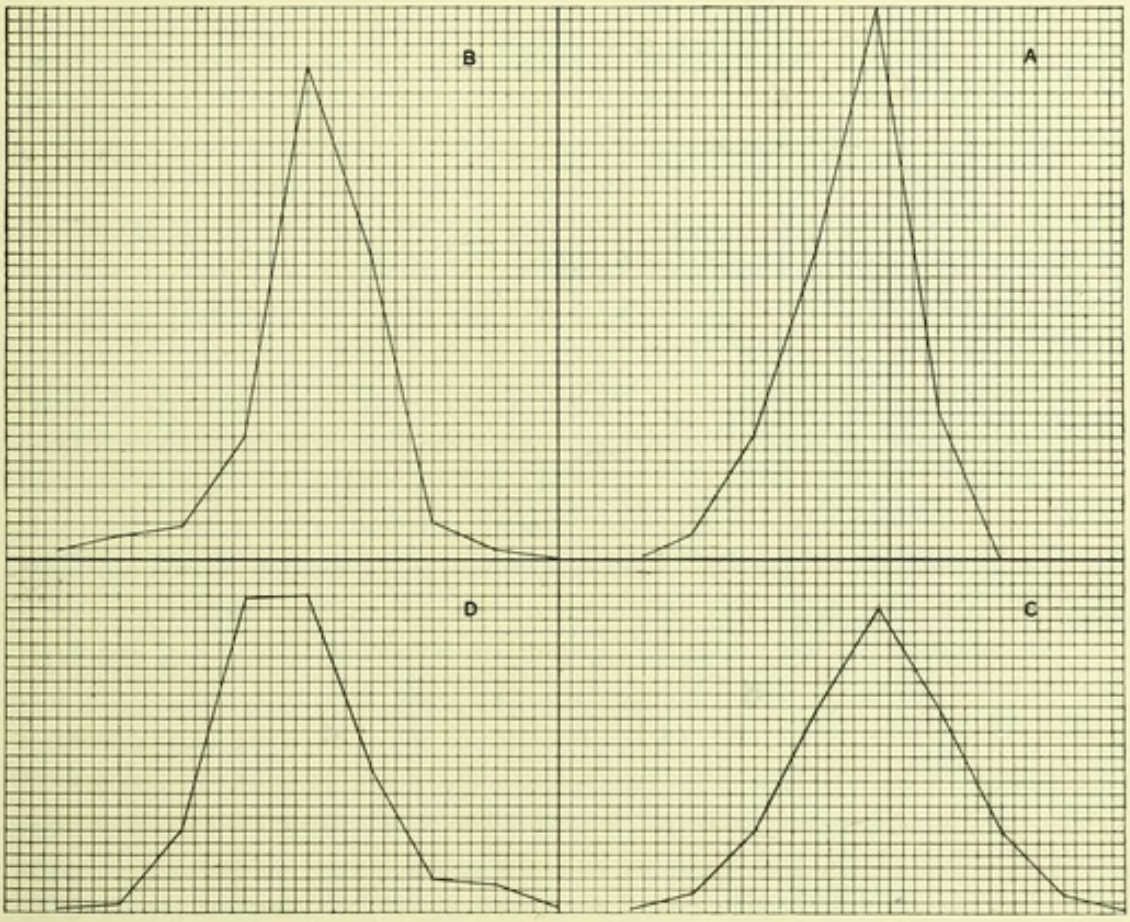

FIG. 1.

A, An epidemic constructed on the hypothesis that the infectivity remains constant and that the disease dies out from lack of susceptible persons; **B**, Epidemic of smallpox in Boston, U.S.A., in 1721, showing epidemic dying out, partly from lack of susceptible people; **C**, Epidemic constructed on the hypothesis that the infectivity decreases at the rate of geometrical progression; **D**, Epidemic of measles in Glasgow in 1808, showing that the decline of an epidemic tends to be longer than the ascent.

the form of epidemic is given which would result if the organism lost infectivity at the rate of the geometrical progression. It is symmetrical, as may be seen, and bears a very considerable resemblance to what is

commonly seen in epidemics. For comparison with this an epidemic of measles occurring in Glasgow in 1808 is given in fig. D. This epidemic can fairly be compared with that of small-pox just referred to, because measles had been absent from Glasgow at that date for a considerable number of years. There was therefore a large susceptible population, and, as the infectivity of measles is hardly less than that of small-pox itself, a similar form of epidemic might be anticipated. The curve, however, is quite unlike that seen in the former instance, and after the epidemic was over, to judge by the subsequent behaviour of measles in Glasgow, there were still plenty of susceptible persons left.

In stating as a law that the organism tends to lose its infecting power at a rate approximating to that of the geometrical progression, it is valuable to know that there are analogies in other parts of the animal and vegetable kingdoms. In the recent book by Professor Minot on growth and death, he shows that the rate of growth of many organisms decreases very rapidly in the early periods of life: thus a child grows in the first month after birth much more than in the second, and so on. In the same way, if the growth of an embryo be traced microscopically, many more cells in proportion to the total number of cells in the embryo may be seen undergoing the process of division in the early days of embryonic growth than in the later stages. It is to be noted that this decline in the rate of growth does not in the later stages of development proceed so rapidly as in the first stages.

The mechanism by which the power of infecting is lost has not been the subject of any assumption hitherto. As the infecting cells are continually dividing, it can easily be conceived that with each division something is lost. The most probable hypothesis is that the power of proliferation, enhanced in some way at the beginning of an epidemic, gradually decreases, and that as the organism loses its power of proliferation the epidemic dies out. As noted above, this loss of power does not in the embryo continue to decrease according to the geometrical ratio in the later stages, but remains at a higher level. Did the same law hold for infecting organisms as has been found to hold for the rate of growth of the embryos of the higher animals, the form which the epidemic would take would be a nearly symmetrical one, but one in which the number of cases at the tail was greater than that given did the law of geometrical ratio strictly hold. Examples of this will be seen later.

To prove directly that organisms vary greatly in infective power is somewhat difficult. The bacteriologist has hitherto confined his

investigations chiefly to the aspect of the virulence or lethal qualities of organisms. In the absence of direct experiment we are forced back on the accidents of infection observed in public-health or fever-hospital administration. As such accidents occur without any control of the conditions, it is often difficult to interpret them correctly and obviously impossible to have a doubtful point reinvestigated. Some facts, however, emerge, and with regard specially to measles the infectivity can be almost directly measured. Again and again patients admitted suffering from one particular disease are subsequently found to have been at the same time incubating measles, the latter infection making its appearance some days after admission to the ward. As measles possesses great infectivity from the beginning, and at the same time is of somewhat indefinite onset, there is as a rule ample time for a ward to become infected before the diagnosis is made. In spite of the fact that in many instances the case is removed on the first day of illness, cross-infection of the ward is very frequent. In the last eight years on thirty-seven occasions cases of measles have developed in wards containing a number of susceptible individuals. The table on p. 250 contains the record of these, and, in addition, the number of admissions to hospital of patients suffering from measles for each month. This number is a rough guide to the epidemic condition of measles in Glasgow. The letter N signifies that a case of measles has occurred in a ward and that no subsequent cases have developed. The letter I signifies that the ward became cross-infected. The meaning of this table is more easily seen when it is synopsised in the two subsidiary tables. In the first subsidiary table the manner in which the ward reacted to the infection of measles is shown in relation to the number of admissions per month, and in the second in relation to the period of the epidemic. It is seen that when these admissions are under fifty per month out of twelve instances infection occurred only four times, or in one third of the total. When the admissions were from fifty to 150 cases per month the condition is exactly reversed, while when the admissions were above 150 cases per month out of thirteen instances infection occurred in every one. In the next table the facts are grouped according as the instance occurred during the rise or decline of the epidemic or the inter-epidemic period, the first month after the crest of the epidemic being included in the rise. During the rise of the epidemic the organism is by far the most infective and least during the inter-epidemic period. One fact of special importance is seen when the last epidemic is considered. This epidemic spread with the greatest rapidity and involved greater numbers

than any in the history of the Glasgow Sanitary Department. The organism was evidently specially infective, though not markedly virulent. On no occasion did a ward to which the poison was introduced escape infection, though we were always on the outlook for incubating cases, and in many instances the affected persons were removed from the ward on the first day of the disease.

TABLE I.—NUMBER OF ADMISSIONS FROM MEASLES FOR EACH MONTH FROM JUNE, 1901, TILL DECEMBER, 1908.

	1901	1902	1903	1904	1905	1906	1907	1908
January ...	—	52 I	5	4[1]	32 N	137 N	9	432 II
February ...	—	15 I	13	12	24	68	11 N	207 III
March ...	—	10	19	44	65	89 I	77 I	145
April ...	—	20	13 I	30	141	84	9	64
May ...	—	45	13	27	165 I	63 N	24	35
June ...	82	46	35	10	131 I	69	20	24
July ...	128	18 I	54	11	13	47	8	16 N
August ...	85	12	47	6	53	18	13	17
September	40 N	— I	57 NII	12	42	13	29	5 N
October ...	43	—	101	27	60	7	154 III	8
November	48	10 N	165	34 N	99	2	253 I	—
December	55 N	3	148 I	34	72 I	9 N	342 III	—

[1] Outbreak of smallpox.

A letter is appended in each month indicating that a case of measles incubating was admitted into a ward. The letter N signifies that the ward was not cross-infected, the letter I that it was cross-infected.

TABLE Ia.—TABLE SHOWING THE NUMBER OF TIMES A CASE OF SOME OTHER DISEASE INCUBATING MEASLES INFECTED OR DID NOT INFECT A WARD, ARRANGED ACCORDING TO THE NUMBER OF ADMISSION OF MEASLES CASES PER MONTH.

Number of admissions per month	0-50 ...	50-100 ...	100-150 ...	150
Ward not infected ...	8 ...	3 ...	1 ...	—
,, infected	4 ...	6 ...	2 ...	13

TABLE Ib.—TABLE SHOWING THE NATURE OF INFECTIVITY ACCORDING AS THE INCUBATING CASE WAS ADMITTED—DURING THE ASCENT OF THE EPIDEMIC, DURING THE DECLINE, OR DURING THE INTER-EPIDEMIC PERIOD.

	Ascent of epidemic	Decline of epidemic	Inter-epidemic period
Ward not infected ...	4 ...	2 ...	6
,, infected	24 ...	2 ...	3

The only other disease which spreads readily in the wards is chicken-pox. The consideration of this, however, loses much of its interest from the fact that there are no data by which the periods of the epidemic prevalence of this disease may be recognized. All that

can be said is that of thirty-six occasions on which the poison was introduced, the wards were cross-infected in twenty. The large number of failures to infect is interesting when it is noted how very infectious this disease sometimes is. The table suggests periods of special infectivity, but the number of instances is not sufficient, in the absence of exact knowledge of the epidemic cycles, to permit of conclusions being drawn. It is, however, to be noted that when the number of instances is summed up for each month of the year the winter months show a slightly larger proportion of infecting instances—a result in accordance with the fact that chicken-pox is usually more prevalent in these months.

TABLE II.—TABLE SHOWING, IN A SIMILAR MANNER TO MEASLES, THE NUMBER OF TIMES A PATIENT WAS ADMITTED INCUBATING CHICKEN-POX, WITH THE CORRESPONDING RESULT.

	1901	1902	1903	1904	1905	1906	1907	1908	Total infected	Total non-infected
January ...	N	—	I	—	—	II	—	N	3	2
February ...	—	N	—	—	—	—	—	—	—	1
March	—	NII	—	—	—	—	N	N	2	3
April	—	I	—	—	—	N	II	—	3	1
May	—	N	N	—	NI	—	N	—	1	4
June	—	—	—	—	—	—	—	N	—	1
July	—	—	—	—	—	—	NI	N	1	2
August	—	—	—	—	—	I	—	—	1	—
September ...	N	—	—	N	—	—	—	—	—	2
October ...	NII	—	—	—	I	I	—	I	5	1
November ...	—	NI	N	—	—	—	I	—	2	2
December ...	—	—	—	N	I	NI	NN	N	2	5

	Infected	Non-infected
Totals, October to February ...	12	11
,, March to September ...	8	13

If the infectivity, then, is lost, the question comes to be, at what rate is it lost? As was seen earlier in the paper, Dr. Farr's original epidemic curve, when analysed, requires that the organism should lose its infectivity at a rate corresponding to that of geometrical progression. Assuming that this is the case, and making certain modifications which require for their development mathematical treatment which cannot be explained here, but which is being published elsewhere, a very close approximation to the form of many epidemics is at once obtained. The assumptions required are: (1) That by some means or other the organism acquires very high infecting power, possibly as the result of some pseudo-sexual process, and that this is lost at the rate above discovered; (2) that the infectivity thus acquired by individual organisms

varies around a mean; (3) that the period during which highly infective organisms are liberated occupies only a small portion, not exceeding one-fourth, of the total epidemic period.

As instances of this epidemic theory two diagrams are given. One of these shows the monthly number of deaths from small-pox in Warrington in the year 1743, the other a milk epidemic of scarlet fever in Glasgow in 1892. These instances have been fitted to the theoretical epidemic distribution which is deduced from the principles just referred to. In both the correspondence of the theoretical curve to the actual

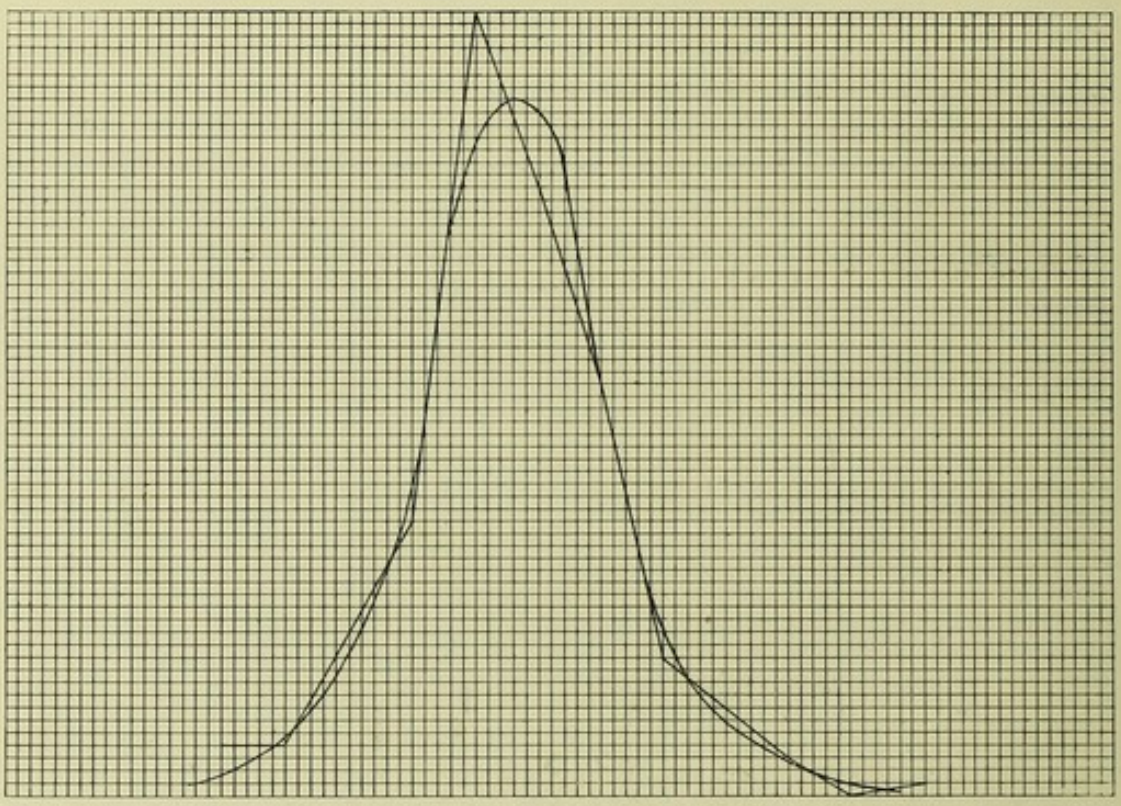

FIG. 2.

Epidemic of smallpox in Warrington, fitted to a theoretical epidemic distribution.

distribution is very close, and these two are but instances of many others. This affords to my mind a considerable amount of proof that the loss of infectivity at the rate of the geometrical ratio on the part of the organism is the main factor in the epidemic disease phenomenon. Of course, it may be equally well explained by a loss of susceptibility on the part of the population proceeding according to the same law, and I can offer no absolute proof that this is not the case. But either explanation relates to a strictly biological process. When we, however, consider

that epidemics are not confined to the lower animal and vegetable forms, but have many analogies among the higher forms, some support is afforded to the former of the two hypotheses. Plagues of locusts,

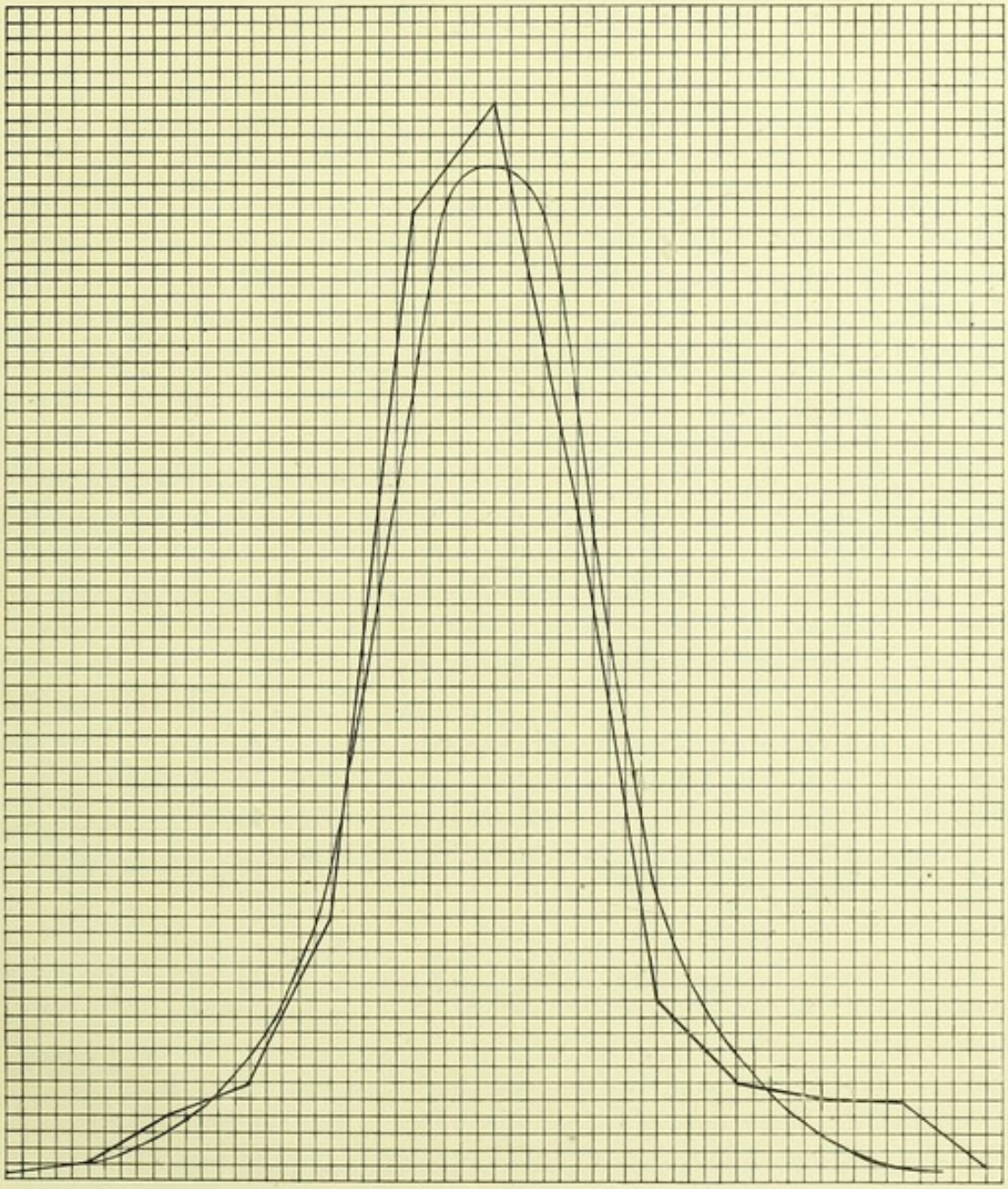

FIG. 3.

Milk epidemic of scarlet fever in Glasgow, fitted to a theoretical distribution.

flies, voles, &c., are well known, and I think that there is little doubt these are phenomena analogous to epidemics. With regard to plagues

of voles, it is recognized by the Commission appointed to inquire into the matter by the Government that for neither their appearance nor disappearance can any satisfactory explanation be offered; in other words, that some increase of fertility of unknown cause takes place, to be followed by a return of this to the normal level.

Epidemics are of two kinds—the seasonal and the solitary. A solitary epidemic is one which occurs at irregular intervals and which starts from a level of the disease, a mere fraction of that reached during the epidemic outburst. Of this type perhaps the most characteristic examples are small-pox and measles. Of the seasonal epidemics, scarlet fever and typhoid fever offer the best examples, and between these stand, as both seasonal and yet conforming to the definition of the solitary epidemic, such diseases as zymotic diarrhœa and plague. Of epidemics in general we have seen that symmetry is a prominent feature, but absolute symmetry cannot be expected of a solitary epidemic. In the case of measles, for instance, the period at which the large schools are invaded would necessarily have a perceptible effect in altering the course. With zymotic diarrhœa the infection might be present in abundance in the soil, and yet the means of conveyance be only irregularly in operation. However, when a composite curve is made for a series of years, it usually happens that the longer the average the more symmetry is attained. This is easily seen by the figures given in the Registrar-General's Annual Summary to be the case for deaths in scarlet fever, while the composite curve of notification from enteric fever for London is another example. Both these are figured in my previous paper, and the illustration need not be repeated here, especially as that for enteric fever is given in Sir Shirley Murphy's Annual Reports, which are in every one's hands. The degree of symmetry is in this case very remarkable.

When the curve of zymotic diarrhœa is examined, however, it is noted to be very markedly asymmetrical. The questions at once present themselves: Is zymotic diarrhœa a specific disease like plague or scarlet fever, or is it spread solely by one means? The answer must at present be doubtful. With regard to the first point, it may be remarked that if two diseases were due to nearly allied organisms the symptoms produced by each might be so closely allied that they would be difficult to separate clinically, or two forms of disease might be recognizable but not yet clinically separated because not looked for.

This difficulty of asymmetry of the epidemic form does not of course necessarily mean that two diseases are present. In the first place, if two

diseases or two modes of spread which act independently be postulated, then two symmetrical epidemics can be arranged to represent the greater part of which is commonly called zymotic diarrhœa. The proof must, however, be sought elsewhere. It is not enough to say that two curves both fulfilling the theoretical epidemic conditions, including symmetry, can be chosen to represent the asymmetric curve of the disease; that might well be an accident. If there are two causes, it is very unlikely that both will always act in the same manner. There should be years when each disease is present almost alone, and also years when both

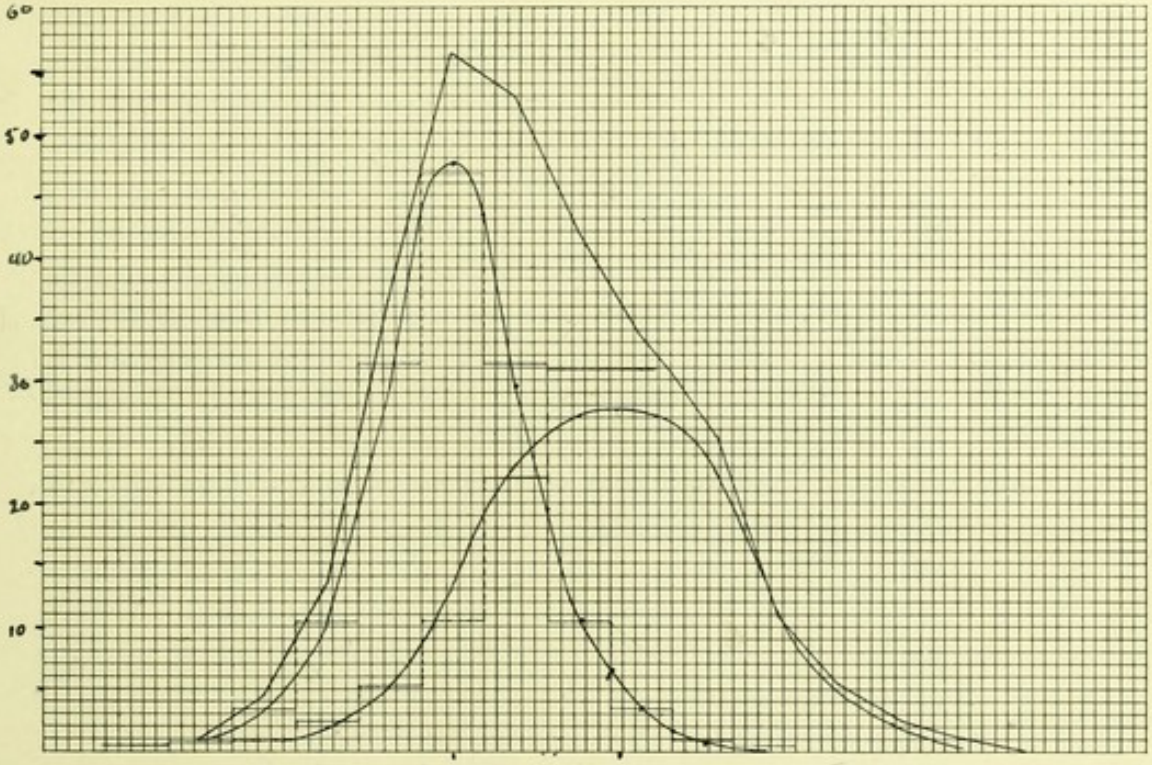

FIG. 4.

Average epidemic of summer diarrhœa in London 1850-1903, fitted tentatively to two theoretical epidemics, as described in the text.

occur together in varying proportions. A study of the disease from year to year should show this, and I think it does. In the accompanying diagram the epidemics of 1895, 1896, 1903, 1907 are given. The first consists almost solely of the early epidemic, the last two equally clearly of the second epidemic, while that of the year 1896 shows a combination of both. For those specially interested the diagrams of Dr. Peters given in his paper earlier in this session may be consulted. Many of the years can be analysed at a glance, and it will be seen that in many years one or

other type predominates. In 1895 almost perfect symmetry of the course is seen. In 1896 the same characteristic is manifest for some time after the crest of the wave has been reached till the rise of the second epidemic is seen, while in the epidemics of 1903 and 1907, both representing the second type, the same symmetry is noticeable. The first epidemic seems to culminate about the thirty-first and thirty-second weeks of the year, and the second from the thirty-seventh to fortieth. The variation in each case is, however, greater than this, and in some cases the first epidemic, being late, runs almost concurrently with an early second epidemic. These considerations help to account for a good many of the vagaries of zymotic diarrhœa. With regard to the clinical side, that there are two diseases I have little evidence to offer. The year 1905 was, however, a year of much zymotic diarrhœa in Glasgow. Both epidemics were present, with a quite distinct interval between them. Dr. David Dickie, who was in charge of the Sick Children's Hospital that summer, says that the August cases were of a quite different type from those at the end of September. The former were more chronic, with evidence of enteritis; the latter more acute, and death ensued in a much shorter time from acute diarrhœa and collapse. With regard to the spread of diarrhœa by flies, the limited evidence at one's disposal is not sufficient to permit of dogmatism, but a few general considerations may be stated. It can hardly be expected, in the first instance, that flies and diarrhœa will have a linear relationship; that is, that they will be in direct proportion. When the number of flies reaches a certain point, a maximum efficiency in causing diarrhœa must be reached. If there are 500 flies in a room it is not probable that chance of infection is twice as great as if there were only 250, unless the percentage of flies causing infection is very small. What relationship or what law it should express is quite unknown. No such case has yet been measured. Dr. Niven's figures for Manchester for the years 1904, 1905 and 1906, however, show some degree of linear relationship between flies and diarrhœa. In that of 1905, for instance, the proportion of flies to diarrhœa deaths is as is given in the following table:—

VALUE OF $\frac{\text{NUMBER OF FLIES}}{\text{DIARRHŒA DEATHS X100}}$ WHEN THE DATES OF ONSET OF ILLNESS ARE TAKEN FOR EACH CASE OF DEATH FROM DIARRHŒA.

Week ending			Week ending		
June 17	...	1·5	Aug. 12	...	1·4
,, 24	...	1·8	,, 19	...	1·4
July 1	...	1·5	,, 26	...	1·6
,, 8	...	2·3	Sept. 2	...	2·2
,, 15	...	1·1	,, 9	...	4·3
,, 22	...	1·3	,, 16	...	3·2
,, 29	...	1·2	,, 23	...	3·7
Aug. 5	...	1·3	,, 30	...	3·4

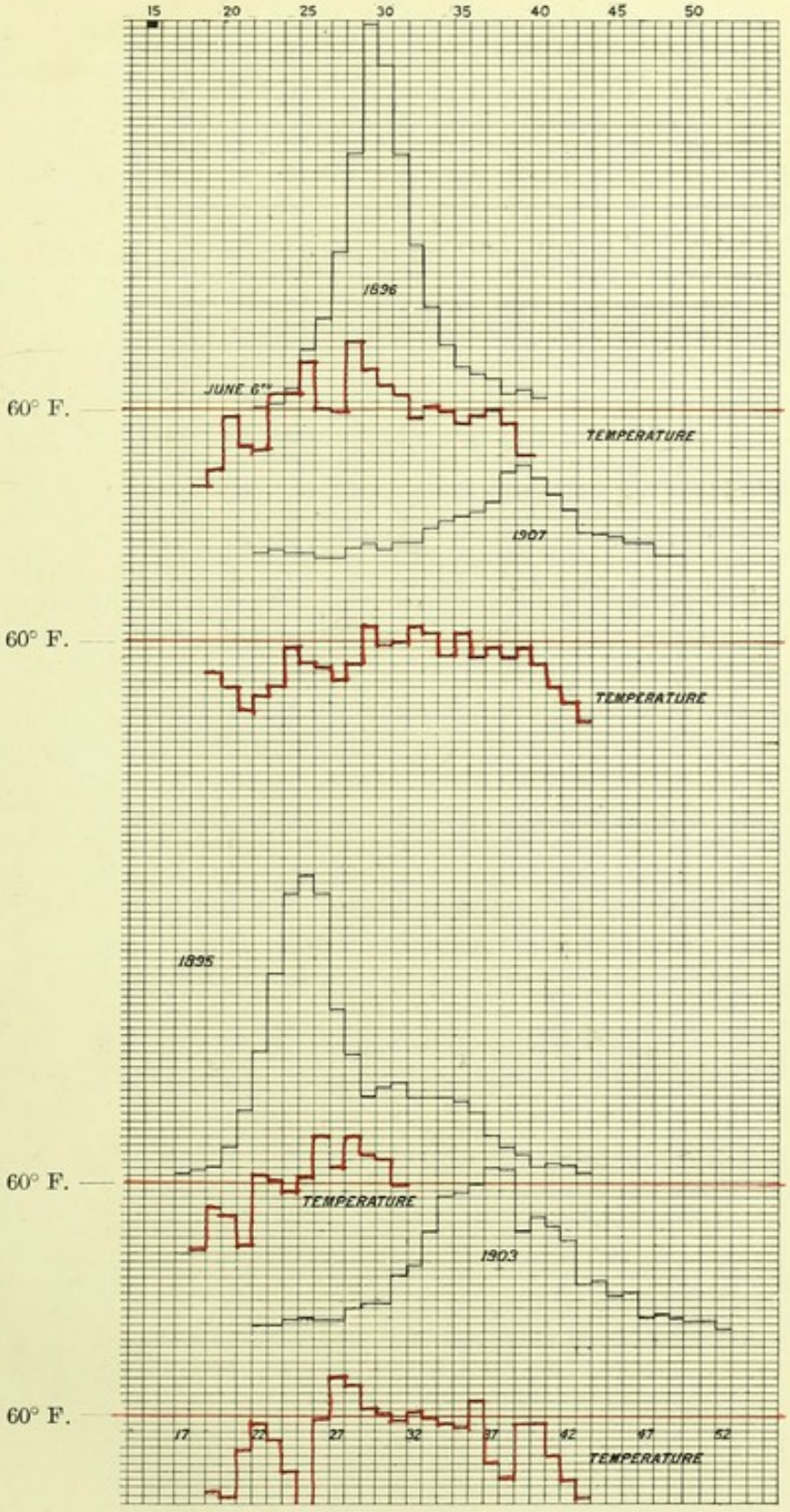

FIG. 5.

Four epidemics of summer diarrhœa in London, charted so as to correspond week by week. To each epidemic the appropriate weekly mean temperature for the year is appended.

Here the principal point which must be noted is that it is at the tail of the epidemic a much larger proportion of flies seems to be necessary to produce a case. This indicates that even if the flies be the carriers there is a want of infective material to convey by the time the epidemic is spending its force. It can hardly be that the flies are much more lethargic in September than they are in June, the temperature of these two months not differing to any great extent. If the diagram of the course of summer diarrhœa in 1895 and 1896 is examined, it will be found that the epidemic in both instances began to fall while the weekly mean temperature of the air was well above 60° F. Dr. Hamer's elaborate investigation into the relationship of flies and diarrhœa in London might be taken also to show that the house fly bred in the dunghill was responsible for the second wave of the disease, while the house fly from other sources was responsible for the primary wave.

Dr. Niven gives no figures for 1907, but it would have been interesting if it could have been noted whether the experience of Manchester coincided with that of London for that year. In spite of the large numbers of flies present during the whole summer, the diarrhœa epidemic was very late in appearing, and its fall preceded that of the fall of the flies. Considering all the facts, it seems to me probable that there are two forms of zymotic diarrhœa, that both tend to run a symmetric course independently of each other, and that though the carrier of the infectious agent be flies, there is a potent factor in the condition of the agent itself.