SOME QUANTITATIVE STUDIES IN EPIDEMIOLOGY.

AN account of some quantitative studies in epidemiology has recently been published in the second edition of my book on the " Prevention of Malaria " (Murray), and the Editor of NATURE has asked me to give a general description of them here. The attempts originated in the following manner. Shortly after Anophelines were shown to carry malaria, it was often observed that little apparent correlation could be found between their numbers and the numbers of infected persons in a locality. The observations were always far too scanty to establish any real absence of correlation; but they were used, nevertheless, to support the thesis that the *amount* of malaria does not depend upon the *number* of the Anophelines, and that therefore the proposed anti-malarial measure of mosquito reduction (then very unpopular) was useless. For many reasons a trustworthy experimental investigation would have been very difficult and costly, and it was therefore all the more necessary to examine the subject by a carefully reasoned analysis of the relations which must hold between the amount of the disease and the various factors which influence it. My first attempt in this direction was made in an official report on the " Prevention of Malaria in Mauritius " (Waterlow and Sons, 1908), and fell into the form of a simple difference equation. This was further developed in the first edition of my book already mentioned, and the subject was at the same time ably attacked by Mr. H. Waite, at the instance of Prof. Karl Pearson, in *Biometrika*, October, 1910.

The attempt now referred to aims at extending the reasoning to infectious diseases in general. The object is as follows. Suppose that a given proportion of a population in a given locality at a given moment are infected with some disease. Then we know from experience that the number will not remain fixed, but will vary from time to time and from place to place. The problem is to calculate these variations on the supposition that all the coefficients are known, which, of course, is by no means always the case. The use of the calculation will be (1) to obtain more light regarding the coefficients by comparing calculated with observed results; (2) to obtain quantitative estimates as to how far each coefficient should affect the result; and (3) to improve preventive measures by showing which factors they should be directed against. My studies have been hitherto concerned only with time-to-time variations, and the reader will understand that they require verification and completion by better mathematicians than myself. So far as I can ascertain, the subject has been little dealt with hitherto.

We must first obtain clear ideas on some points. Infectedness is not the same thing as sickness. *Infectedness* begins when the infecting organisms first enter the body of the host (man, animal, or plant), and ceases only when the last of them die out of him or leave him, or when he himself dies. *Sickness* may be quite absent during the whole of this period, or may begin after an " incubation period "; may cease long before or long after infectedness ceases, or may be intermittent. It is therefore merely an episode of infectedness, and one which does not concern us greatly just now. Another episode, and a more important one at the moment, is *infectiveness*, that is, the state of the infected person during which the infecting organisms are able to pass from him to others. The period or periods of infectiveness are always contained within the period of infectedness, but do not necessarily coincide with the periods of sickness. Thus typhoid or diphtheria carriers may be ill for only a week or so, or not at all, but may remain infective for months. In yellow fever, according to good researches, sickness and infectiveness begin together a few days after the commencement of infectedness at inoculation; but infectiveness ceases three days later, often long before the sickness is over. In malaria, sickness and infectiveness are intermittent and not coincident episodes, and may recur for years. Infectedness itself is only the preliminary stage of *affectedness*, which begins at inoculation and does not end until the last trace of the resulting sickness or acquired immunity has vanished. Reinfection often occurs during existing affectedness, and may increase its dura-

tion and that of the episodes. Medical treatment may have the opposite effect, and natural immunity and prevention may reduce susceptibility to infection. Lastly, the natural fluctuations of population, due to births, deaths, immigration, and emigration, must be considered, and these may vary in consequence of the epidemic.

Hence many coefficients have to be taken into account; and the principal difficulty lies, I fancy, in arranging for all of them in the equations. The course which I have adopted as being perhaps the best for a beginning is to conceive the matter in the most general terms possible by taking the act of infection as being one of any kind of event, such as accident, death, marriage, bankruptcy, receipt of bequests, insect-bite, &c., which may occur to a population, the various coefficients being at present taken as constant during the period considered. If such an event occurs to a given constant proportion of the population in unit of time, how many affected people will there be in the locality on a given date, on a most probable estimate, and how many of these have been affected once, twice, thrice, &c.? This simple form may be called the problem of *happenings*, and its solution will often be useful in epidemiology, as, for instance, in estimating the most probable frequency of reinfections or of insect-bites. But for some kinds of events, such as marriage, wealth, and infectedness, we must contemplate a continuance of the event in the individual, with a possible reversion to the unaffected class after the cessation of affectedness. Such events may be called *becomings*; and we have now to find the proportion of the population in this condition on a given date.

I will treat the equations as briefly as possible. Consider the following:—

$$a_{t+1} = (1-h)va_t + HVz_t$$
$$z_{t+1} = h\,va_t + (1-H)Vz_t$$
$$p_{t+1} = va_t + Vz_t . \quad . \quad . \quad . \quad . \quad (1)$$

Here a_t and z_t are respectively the numbers of unaffected and affected individuals, and p_t is the total population at the end of t units of time; v and V are respectively the variations in number of the unaffected and the affected due to births, deaths, immigrations, and emigration in unit of time; h is the proportion of the unaffected which become affected, and H the proportion of the affected which become unaffected (to be better defined presently) in unit of time. Thus $1-h$ and $1-H$ are respectively the proportions which remain unaffected and which remain affected, and a_{t+1} and z_{t+1} are the numbers of the groups after the lapse of one unit of time. The gain of one group is the loss of the other group, and the total population is the sum of the two groups, the factors h and H disappearing in the summation.

If n, m, i, e denote the (constant) nativity, mortality, immigration, and emigration rates among the unaffected, and N, M, I, E the similar rates among the affected, it is correct, I believe, to write $v=(1+n)(1-m)(1+i)(1-e)$, and a similar equation for V. Different symbols are necessary for the two groups, because all the quantities, even the immigration, may differ. We now take the equations in more exact detail, but omitting v and V for the moment. Thus

$$a_{t+1} = (1-h)a_t + (1-h)na_t + (1-h)Nz_t + (1-h)rz_t$$
$$z_{t+1} = h\,a_t + h\,na_t + h\,Nz_t + h\,rz_t + (1-r)z_t$$
$$p_{t+1} = a_t + na_t + Nz_t + z_t . \quad . \quad . \quad (2$$

Here n and N are the birth-rates of the two groups. The second and third columns give the happenings among the births; rz_t is the proportion of the affected which *revert* to the unaffected group in unit of time, and hrz_t the (very small) proportion of these which immediately become reaffected; $(1-r)z_t$ is the proportion of the affected which do not revert, and $(1-h)_1z_t$ the proportion of the reverted which are not immediately reaffected. Obviously p_{t+1} is merely the sum of the two groups a_t and z_t *plus* the births that have occurred to both in the unit of time, and the symbols h and r disappear in the summation. The equations are not symmetrical, because, though the progeny of the unaffected are born in this group and belong to it, the progeny of the affected are not born affected, and therefore do not belong to the latter group. I think that this is the better arrangement; but it would be possible

to add a term for affected births, as in syphilis. The first two of the above equations may be written

$$a_{t+1} = (1-h)(1+n)a_t + (1-h)\frac{N+r}{1+N}(1+N)z_t$$

$$z_{t+1} = h(1+n)a_t + \left\{1 - (1-h)\frac{N+r}{1+N}\right\}(1+N)z_t \quad (3)$$

If, now, we restore the mortality, immigration, and emigration rates, that is, affix to a_t in both equations the coefficient $(1-m)(1+i)(1-e)$ and to z_t the coefficient $(1-N)(1+I)(1-E)$, we have

$$a_{t+1} = (1-h)va_t + (1-h)\frac{N+r}{1+N}Vz_t$$

$$z_{t+1} = h\, va_t + \left\{1 - (1-h)\frac{N+r}{1+N}\right\}Vz_t . \quad . \quad . \quad (4)$$

which are obviously the same as equations (1) if H is now defined as the value of $(1-h)(N+r)/(1+N)$.

The complete solution of these difference equations is

$$(X-Y)a_t = (a_1 - a_0 Y)X^t - (a_1 - a_0 X)Y^t$$
$$(X-Y)z_t = (z_1 - z_0 Y)X^t - (z_1 - z_0 X)Y^t$$
$$(X-Y)p_t = (p_1 - p_0 Y)X^t - (p_1 - p_0 X)Y^t \quad . \quad . \quad (5)$$

where

$$a_1 = (1-h)va_0 + HVz_0 \qquad z_1 = hva_0 + (1-H)Vz_0$$
$$p_1 = va_0 + Vz_0 \qquad\qquad p_0 = a_0 + z_0$$

and X and Y are the roots of the auxiliary algebraic quadratic equation

$$x^2 - \{(1-h)v + (1-H)V\}x + (1-h-H)vV = 0.$$

These roots are rational for several particular values of the constants. The most important instance is when $v = V$, that is, when the happening does not affect the normal fluctuations of the population. Here $X = v$ and $Y = (1-h)(1-r)/(1+N)$, and

$$z_t - Y^t z_0 = \frac{h(1+N)}{N+r+h-hr}(p_t - Y^t p_0). \quad . \quad . \quad (6)$$

As Y is in this case less than unity, Y^t diminishes without limit as t increases, and therefore z_t, the number of affected individuals, asymptotes to a fixed proportion of the total population, provided that all the elements remain constant. I call this proportion the *static value*. In disease it gives what is called the *endemic index*, or *ratio*.

In epidemiological applications the symbol z refers, not to sickness or even infectedness, but to affectedness as defined above; and the symbol r does not mean recovery from sickness or infectedness, but reversion to a susceptibility to a fresh happening (inoculation), that is, to loss of acquired immunity. Thus in drawing curves of epidemics we must remember that this last factor may not come into play until long after the commencement of the epidemic, or not at all.

In my book the above equations are treated also in the infinitesimal form, when the integrals become exponential. Thus the second of equations (2) becomes

$$\frac{dz}{dt} = h(p-z) + qz,$$

where $q = V - 1 - r - N$. If the total population p remains constant, this is easily integrable if h is also constant, or (what more probably happens in epidemics) is a linear function of z, say cz.

Numerous applications are possible; but I have space to refer only to the important case of "metaxenous diseases," that is, to infections common to two species of animals or plants. The same equations apply to both species, but the happening-factor h in one equation must be a function of z in the other equation. We thus have two simultaneous equations to solve, namely,

$$\frac{dz}{dt} = k'z'(p-z) + qz$$

$$\frac{dz'}{dt} = kz(p'-z') + q's'$$

where the marked symbols apply to one species of animals (say, mosquitoes) and the unmarked ones to the other

species (say, man), and k and k' are constants composed of the most probable frequencies of communication between the two species, of infectivity and of natural immunity. Prof. F. S. Carey has referred these equations to Prof. A. R. Forsyth, who thinks that they are not likely to be easily integrable in finite terms; but the most important case is where both z and z' have reached static values, when the differential coefficients vanish. We then obtain at once

$$z = \frac{kpk'p' - qq'}{kk'p' - kq}$$

with the similar equation for z'. In the case of some insect-borne diseases this becomes (reduced)

$$z\{(1-r)fb'f'b'A + rfb'\} = p\{fb'f'b'A - rN'\},$$

where z is the ratio of affectedness among men (say), f and f' the proportion of infective men and insects, b' the frequency of bites, r the reversion rate among the human patients, N' the birth-rate of the insects, and A the ratio of the number of the insects to head of human population. Numerical estimates of the constants in malaria are attempted in the book, and a table of calculated values of A for various values of z and b' are given (as already partly done by Mr. Waite).

The following important laws seem to be established:— (1) the disease (z) will not maintain itself unless the proportion of Anophelines (A) is sufficiently large; (2) a small increase of A above this figure will cause a large increase of z; and (3) z will tend to reach a fixed value, depending on A and the other constants. I doubt whether these laws could have been reached except by such mathematical attempts. The second one is especially important. If A is just at the critical value, z will be zero, or only just above it; but if A is only about double this critical value, a serious epidemic, amounting to about half the whole population, may follow. Yet such a small increase in the number of Anophelines will scarcely be detectable except after very careful study, a fact which easily explains why marked correlation has not always been observed. The same equation shows that, if certain experiments are to be trusted, yellow fever can scarcely be considered an endemic disease of men at all; and it also explains the absence of certain diseases in the presence of capable carriers, and the general phenomena of smouldering epidemics.

The most probable numbers of individuals to which a happening has occurred never, once, twice, &c., can easily be obtained, and are equal to the successive terms in the expansion of $\{(1-h) + h_t'V^tp_0$ in ascending powers of h. This enables us to estimate the number of persons who have been bitten, or the number of insects which have succeeded in biting never, once, twice, &c., in a given period, and to calculate the average number of bites received or inflicted by each individual. It also enables us to calculate (what I think has not been done before) the frequency of *reinfections*. At present such reinfections are not much considered during the course of an already existing infection, but I estimate that in a locality where half the people are statically affected with malaria no fewer than about 63 per cent. will be infected or reinfected every four months (under constant conditions). In 1898 I showed that birds reinoculated with malaria could exhibit renewed and severe infections.

Lastly, to complete the study, it is necessary to estimate the most probable proportion of affected individuals who are also infected, or infective, or sick at a given moment. This will be the same as the proportion of the average number of days lived during these "episodes" to the average number lived during the whole period of "affectedness," which can be calculated from the special pathological data.

These studies require to be developed much further; but they will already be useful if they help to suggest a more precise and quantitative consideration of the numerous factors concerned in epidemics. At present medical ideas regarding these factors are generally so nebulous that almost any statements about them pass muster, and often retard or misdirect important preventive measures for years.   RONALD ROSS.