



## Epidemiologic Models in Studies of Vector-Borne Diseases

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THE CENTER of interest and point of emphasis of any living subject changes. The center of active interest in epidemiology gravitates to the United States of America, and I pay homage to the outstanding quality and volume of work I have seen in this country. It is therefore a unique privilege to give the Dyer Lecture at the National Institutes of Health, and especially to do so in the presence of Dr. Rolla E. Dyer, who is largely responsible for the stature of the Institutes and after whom the lecture is named.

An epidemiologic model is a closely argued statement of the quantitative aspects of transmission of a disease. This model includes all those factors with a direct influence on the dynamics of transmission and shows proportionately, but not necessarily in exact numerical terms, how changes in any one or all of the factors will influence transmission, incidence, and prevalence.

The model taken by itself has no significance; it proves nothing and explains nothing, except perhaps the mind of the man who made it. Its value lies in its potential use as a tool for understanding the patterns in which the disease occurs, the causes of divergence between them and of fluctuations in prevalence, the rel-

ative significance of individual factors and of changes in their values, for checking biological knowledge, and for analyzing its completeness for epidemiologic purposes.

Study of malarial infections was originated by Farr (1, 2), who successfully fitted a smoothed curve on a smallpox epidemic and later predicted the probable future course of an epidemic of rinderpest on the basis of a mathematical examination of past happenings. This method of predicting the course of infections was elaborated in relation to direct infections by Brownlee (3), Hamer (4), and others, and by Ross (5, 6) in relation to infections conveyed by an intermediate host, the mosquito. From about this time, 1906, an active literature on the subject flourished, culminating in the monumental work of Lotka (7), but the subject then went into a state of suspended animation, with very little literature after that date until after World War II, largely because the models produced had not in fact served as useful tools in the understanding of natural happenings. Notably the theoretical models of direct infections showed a small but consistent difference from natural epidemic curves, while those of malaria required, to simulate nature, the attribution of values to constants which no malariologist would accept as realistic.

The study of both types of infection has since been revived, and realistic models of direct and indirect infections are now produced.

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*Dr. Macdonald, director, Ross Institute of Tropical Hygiene, London, England, delivered this lecture November 15, 1960, at the National Institutes of Health, Public Health Service.*

In the case of direct infections it has been shown that deterministic models such as were developed by earlier workers are not properly applicable to the transmission of infections in communities which are subdivided into innumerable cells by the facts of housing and town life, whereas stochastic models can be appropriately developed for them. In the case of the indirect infections it has now been realized that some of the basic definitions on which earlier workers relied were inaccurate; their correction makes possible the production of realistic models, which have been elaborated in relation to malaria (8-12). Moreover, the deterministic technique remains applicable to many cases of these infections, perhaps because their dissemination by migrating insects blurs the barriers to transmission from house to house. The use of these definitions has thrown much light on the epidemiology of malaria. Particularly they have shown the existence of true epidemiologic patterns in what had previously been an endless series of widely varying pictures, and they have demonstrated the relative importance of changes of value in the various factors influencing the extremely complicated chain of transmission. I now consider them an indispensable aid in the understanding of any of the indirect infections.

The methods involved in the mathematical analysis are not abstruse, and the technique is well within the mathematical power of many biologists. The difficulty of the subject to a biologist lies in directing his thoughts into the wholly quantitative channels of dynamics, in lack of acquaintance with the type of steps involved in building up a complete model, and in the lack of apparent meaning in the ultimate product of some previous studies which have been left in their mathematical form without back translation into biological terms. To the biometrician they present no technical problems whatever; his difficulties lie in recognizing the needs of the epidemiologist and the type of analysis which might be helpful to him.

My present lecture is an exercise in translation, an effort to explain what steps may be helpful in creating a model, what factors need to be taken into account in each model, how the models integrate with one another, and the type

of information which may be derived from them. I will use malaria for demonstration of these steps, but I hope to show that the principles can be applied to other conditions, and what type of modification is necessary to do so. The process falls into three stages, each of which may have a number of subdivisions: (a) the formulation of a general scheme showing what factors are directly involved in the dynamics of transmission; (b) the arrangement of one's ideas to form such combinations of these factors as are logical and germane to the subject, and (c) the examination of the steps of transmission, first as a series of isolated events, and then as a working mechanism in which the movement of one cog affects another, and so to form a complete picture.

A biological picture has to be converted into quantitative terms to form the general scheme. Figure 1 illustrates the transmission cycle of malaria. Within the circle the cycle is shown in traditional form, from schizonts through gametogenesis, fertilization, sporogony, inoculation into man, and the exo-erythrocytic cycle back to schizogony. Outside the circle are the quantitative aspects of these happenings. Infection in man has the characteristics of duration and infectivity, both of which can be expressed numerically. The infective patient is bitten by mosquitoes which have the characteristics of numbers, frequency of biting man, susceptibility to malaria, and longevity; the sporogony cycle has the characteristic of time, which may be used to subdivide the mosquito's pattern into a probability of survival to infectivity, and subsequent expectation of life should it do so. Sporozoite-infected mosquitoes have a certain average infectivity, though it

Figure 1

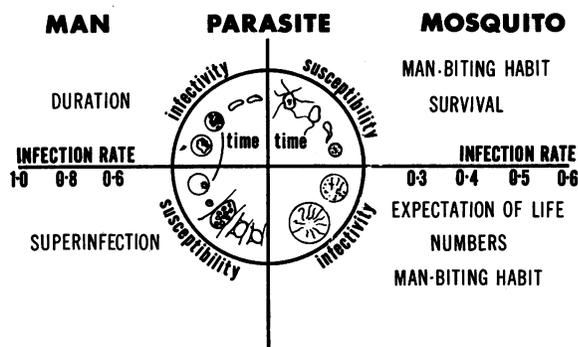
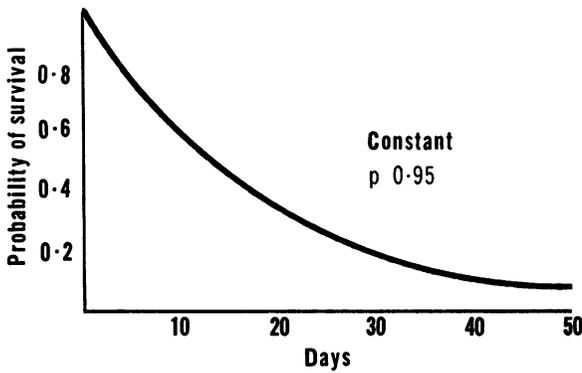


Figure 2. Survivors from a constant mortality rate



Probability of survival to $n$ days	$p^n$
Expectation of life	$\frac{1}{-\log_e p}$
Number of feeds on man	$\frac{a}{-\log_e p}$

Where  $a$  is average daily feeds

can be measured only in conjunction with the susceptibility of man. Finally, a characteristic of new infection in man is that it can often be superimposed on a previous infection. The interaction of these characteristics produces ultimately one infection rate in man and another in the mosquito. It will be convenient in several later diagrams to adhere to the general form used in this one, because it visually relates a given infection rate in man on the left, through the upper semicircles, to one in the mosquito on the right, and the infection rate in the mosquito through the lower semicircle to a rate in man again.

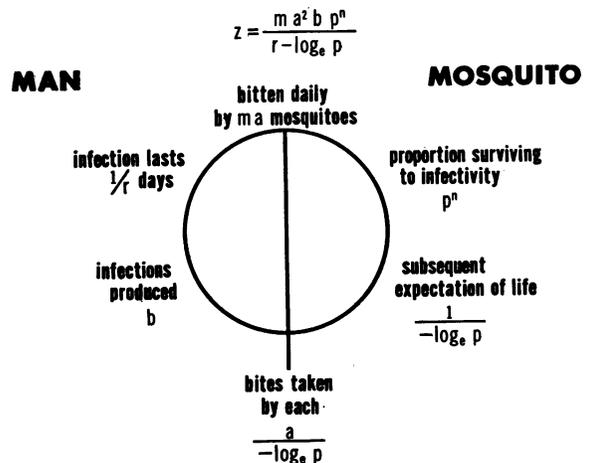
The second step is the formation of appropriate combinations, or derivatives, of these basic factors. One such set of derivatives is shown in figure 2. It is a reasonable, though not exact, representation of natural happenings to consider the mortality of anophelines as unrelated to age. On this basis it is possible to express for any given probability of survival through 1 day ( $p$ ) the probability of survival for any given number of days, such as the time of sporogony ( $n$ ), and the expectation of life of a mosquito from any age at which it is known to be alive. A combination of this expectation of life with the probability of biting man on any

one day ( $a$ ) gives the total number of bites on man taken by the average mosquito during its whole lifetime, the great significance of which is brought out in mathematical working and which therefore deserves a title for easy reference. It may be termed the "total biting figure."

Another important combination is the basic reproduction rate, or number of infections which would be distributed by a single patient with a primary case of malaria if no infections were blocked by previous infection of mosquito or man. The concept, illustrated in figure 3, is quite simple. If the probability of recovery on any day, or the recovery rate, is  $r$ , the duration of infectivity is  $1/r$  day. The patient with the primary case is bitten on each of these days by  $ma$  mosquitoes,  $m$  being their numbers in relation to man and  $a$  being the probability of their biting man on any one day. The probability of their survival to infectivity ( $p^n$ ), and the number of subsequent feeds on man by those which

survive for this period  $\left(\frac{a}{-\log_e p}\right)$  can be derived from figure 2. A proportion ( $b$ ) of these feeds will actually implant infection. Simple multiplication of these gives the basic reproduction rate. This is a concept only, many of these infections in nature being blocked by previous infection of the mosquito or man. Its full justification lies in the fact that expressions worked with fully rigorous allowance for the basic reproduction rate can often be simplified

Figure 3. The basic reproduction rate



by substitution of this identity, which is adequate proof of its value as a concept.

The third step is to examine the dynamics of transmission, and for this there are needed:

- An expression for the dependence of the mosquito infection rate on a constant inoculation rate in man.
- The converse expression for the dependence of the human infection rate on a constant inoculation rate.
- An expression for the way in which these rates mutually adjust to each other when both are free to change, an increase in one causing a corresponding rise in the other and so ad infinitum, though in progressively smaller stages till virtual equilibrium is reached, which the expression should represent.
- Some expression or representation of the sensitivity of this equilibrium to changes in its controlling factors.

Figure 4

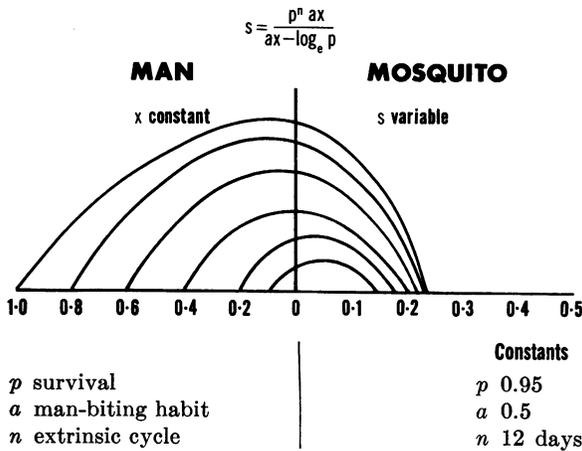


Figure 5

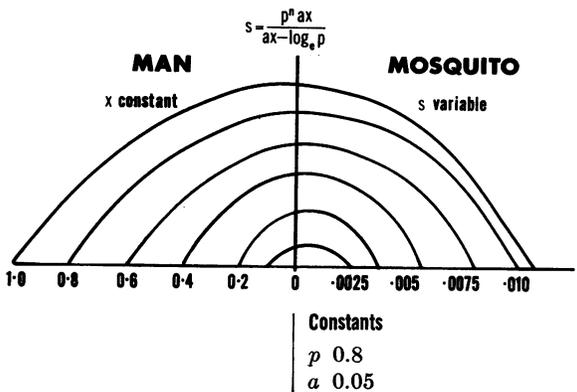
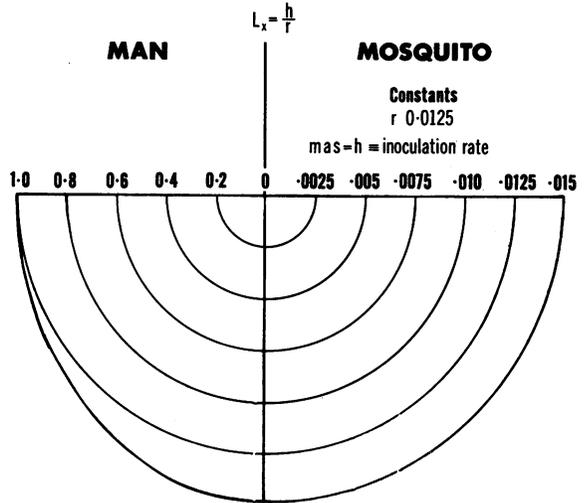


Figure 6



These expressions will, so far as appropriate, be illustrated by two contrasting examples, in one of which the anopheline carrier is given a high total biting figure, and in the other a low one.

Figures 4 and 5 illustrate the effect of a constant human infection rate ( $x$ ) on the mosquito infection rate ( $s$ ), the symbols  $p$ ,  $a$ , and  $n$  having the meanings given previously. The ruling expression, derived from Macdonald (10), is given at the head of the figures. Figure 4 shows the relationship when the total biting figure is high, 9.25, being determined by high values of both the biting habit and longevity, such as are typical of *Anopheles gambiae*. An increasing human infection rate causes a disproportionately small increase in the mosquito infection rate; or a high total biting figure restricts the correspondence between the two infection rates. Figure 5 refers to happenings when the total biting figure is low, 0.224, being determined by low values of both biting habit and longevity, such as are characteristic of *Anopheles culicifacies* in parts of India. The actual values of the mosquito infection rate are much lower than in the previous example and are shown on a different scale, but in this case an increase in the human infection rate is matched by an almost exactly proportionate increase in the mosquito infection rate; a low total biting figure permits almost complete correspondence between the two infection rates.

The inoculation rate ( $h$ ) depends on the in-

fection rate in mosquitoes ( $s$ ), their numbers ( $m$ ), and the frequency with which they bite man ( $a$ ). If all of these are constant, and allowed to operate for sufficient time, during which immunity is not enhanced, the resultant human infection rate will gravitate toward a limiting value ( $L_x$ ) in which the only other component is the recovery rate ( $r$ ), and this limiting value is in direct proportion to the value of the inoculation rate until infection is general (fig. 6). This simple form differs from that seen in most infections. It is decided by the fact that superinfection occurs, and the method of its mathematical handling was shown by Irwin in a paper by Macdonald (8).

If both the infection and inoculation rates are variable, an increase in one causes a corresponding increase in the other, and so on indefinitely, but in steadily decreasing degree, till the two rates approach a limiting value, shown in the expressions at the head of figure 7, which itself is diagrammatic only. The possible range of the human infection rate extends from 0 to 1.0, and that of the mosquito infection rate from zero to  $p^n$ . The full expressions for the limits are lengthy, but it is possible to simplify them to the forms shown by insertion of the identity for the basic reproduction rate. The human infection rate is determined by the total biting figure, which occurs in a reciprocal form, and the reproduction rate. The mosquito infection rate is determined by the reproduction rate and the probability of survival to infectivity ( $p^n$ ). It will be noted that, if the reproduction rate ( $z$ ) is put at 1.0 or less,

Figure 7. Limiting values

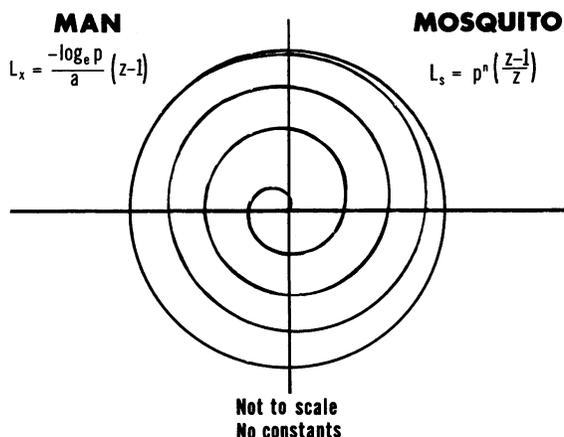


Figure 8

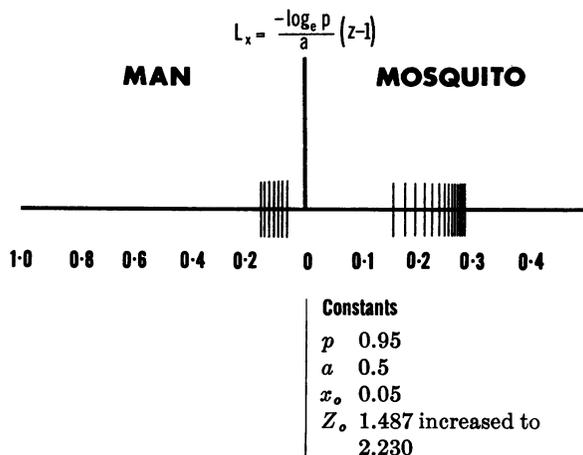
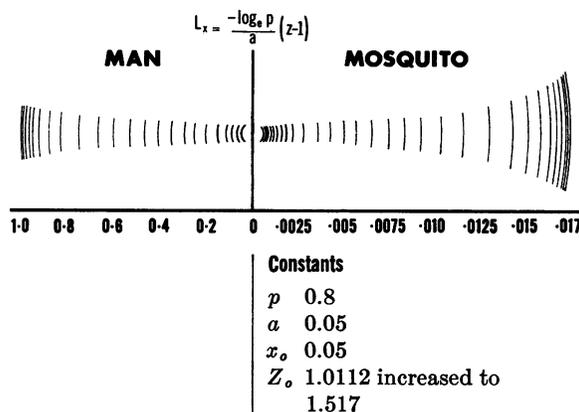


Figure 9



both of the infection rates become 0 or unreal, and this is the basis of the concept of the critical level of transmission, below which the disease disappears, as in anophelism without malaria. With long-standing transmission the basic reproduction rate would itself undergo change, on account of the reduction in the duration of infections owing to the development of immunity, and this is the reason for omission of any numerical statement of these expressions in the diagram.

Examination of the concept of these limits can nevertheless be very fruitful. This may best be illustrated by examination of the degree of change in the two limits produced by alteration of the basic reproduction rate. This is shown for the two extreme cases in figures 8 and 9, which are on the same principle as previous diagrams though the connecting links

between the two sides have been eliminated for the sake of simplicity. The first concerns happenings when the total biting figure is high, 9.25, as used in figure 4. It is assumed that the human infection rate had previously been stabilized at 5 percent, and the fact that immunity may have played a part in this is irrelevant. The basic reproduction rate is then assumed to have increased by 50 percent, and the changes in the two infection rates are followed through their successive increases to their new limiting values. In figure 9 the same series of happenings is followed, but the total biting figure involved here is small, 0.224 as in figure 5.

The two sets of happenings are quite distinct from each other. In the first case the two infection rates increase by small steps, the human one gaining stability again at 12.6 percent. In the second, both rates increase by progressively larger steps until saturation is approached, and the human rate does not settle down until it reaches 100 percent. These figures show diagrammatically the working of stability, instability, and equilibrium, for which the full proof lies in complete mathematical working. A high total biting figure results in a stable infection rate which is relatively insensitive to changes in the controlling factors, whereas a low total biting figure determines a very unstable state of equilibrium which is drastically upset by small changes in the transmission. Any of the factors which enter into the reproduction rate may of course determine this change, but the degree of effect on the infection rates is determined solely by the total biting figure.

This picture has been presented in a precise mathematical form elsewhere (11), the present statement being an effort to translate it into simpler terminology. It accords well with natural happenings, both as regards variations in the stability of the disease, and association of this variability with anopheline characteristics. Figure 10 shows the endlessly repetitive seasonal malaria of Italy before its eradication, transmitted by *Anopheles labranchiae* which feeds commonly on man and lives long, while figure 11 shows happenings in Ceylon, also before eradication of malaria, where the disease showed haphazard and extreme variation, great

Figure 10

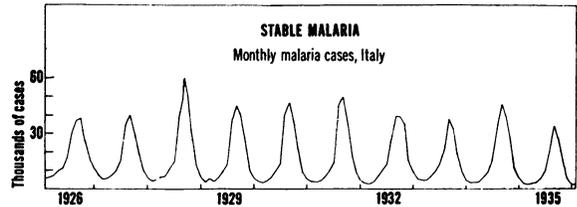
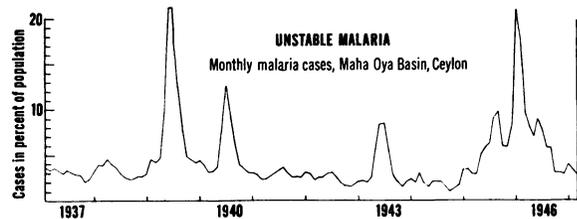


Figure 11



epidemics following minor changes in transmission, under the influence of *A. culicifacies*, which has characteristics of biting and longevity similar to those used in preparing figures 5 and 9.

Examination of a mathematical model can also throw valuable light on the theory and practice of control measures. The effect of control of the breeding is shown in figure 12. Variations in mosquito density produce a directly proportionate change in the reproduction rate, as can be seen by examination of the expression at the head of figure 2. A great reduction in density must therefore be attained if an originally high reproduction rate is to be lowered below the critical level.

However, it may also be seen from the expression at the head of figure 2 that mosquito survival ( $p$ ), representing differences in expectation of life, enters into the reproduction rate twice, and in a complicated form. Figure 13 shows the effect of changes in this expectation of mosquito life. It is assumed that within a given set of values of mosquito density and biting habit, an expectation of 20 days ( $p=0.95$ ) had sustained a reproduction rate of 1,000—a realistic figure. Reduction of this expectation produces a corresponding decrease in the reproduction rate, but on a vastly greater scale, till when it reaches 2.6 ( $p=0.68$ ) the reproduction rate sinks below its critical level and full control is achieved.

The immense success of imagocidal control

came as a surprise to malariologists, but it is explained and could have been foreseen by examination of models of this sort. It would be wise to examine the theory of controlling other diseases, to search for the most effective techniques and not merely allow their possible development by chance.

To what other mosquito-borne infections can this model be applied? None. But its mechanism can be modified and adjusted, with appropriate parallel biological criticism and study, to give comparable information about any other, and I briefly examine the forms of change which would be needed for application to filarial and virus disease transmission.

The scheme of filarial disease transmission differs in that it often kills the mosquito, in which the infective stage lasts for only a short period, so that a different expression is needed for the dependence of the mosquito infection rate on that in man. So far as present biological knowledge goes, the dependence of the human infection rate on the mosquito infection is in identical form with that of malaria, controlled principally by the occurrence of superinfection. However, in the series of data which I have examined there has been a great discrepancy between the apparent inoculation rate shown by entomological study and the effective rate deduced from the age incidence of infection in man, the one being several hundred times as high as the other. The cause might be either that the biological picture inserted is wrong, or

Figure 12. Mosquito density and reproduction rate

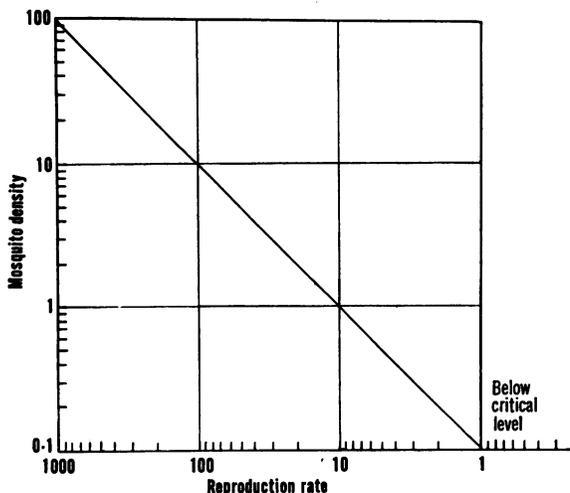
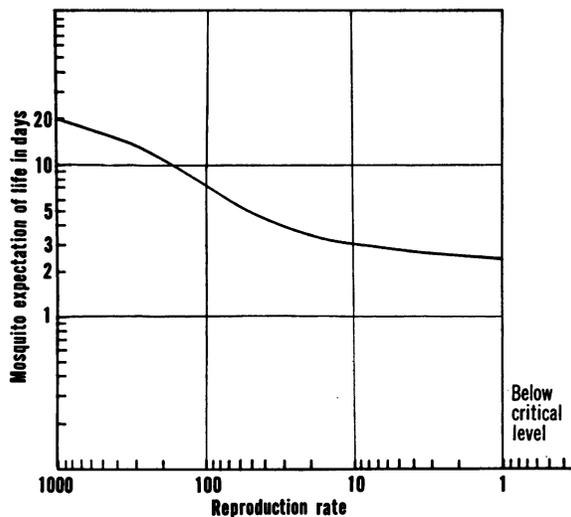


Figure 13. Mosquito expectation of life and reproduction rates



that an extremely low value should be attributed to the infectivity factor, termed "b" in the malarial equation. I have not seen this commented on in the literature and feel some exploration of this subject is essential to the reliability of models of filarial infection.

Since coming to the United States I have been impressed by the interest in mosquito-borne virus infections and have tentatively explored the production of an appropriate model, outlined in the section "Mathematical Background," but it has been tentative only and applies to a hypothetical condition, the verisimilitude of which would require a considerable check. The general scheme of dependence of the mosquito infection rate on the rate in vertebrates is identical, the same considerations apply, an incubation period is involved, and the infection, which does not kill the insect, lasts for the remainder of its life. The scheme of dependence of the infection rate in vertebrates on the infection rate in the mosquito is, however, radically different. Superinfection does not occur; neither in my hypothetical case does reinfection, though it could readily be allowed for. The infection may kill a significant proportion of those infected, and the high immunity developed restricts the possibility of new infections, the frequency of which is closely influenced by the proportion of new nonimmune arrivals, by birth or other means, who



snail. Progress is impossible unless it is made in four stages: the dynamics of happenings in man, in the first free-living aquatic stage, in the snail, and in the second aquatic stage. The essential governing factors in each of these stages are shown in the figure, within the circle so far as they are attributes of the nematode alone and outside it when they are partly or wholly characters of the medium.

Logically the first step is to assume a constant rate of contamination of water with miracidia and to examine the factors which convert this into an inoculation rate of the snails which it contains. The logical and mathematical process is simple and results in the expression

$$h = \frac{kc}{1+ks}$$

where  $h$  is the probability that a snail will be penetrated by a miracidium in unit time, or rate,

$c$  is the number of miracidia liberated in unit volume of water in unit time, or contamination rate,

$s$  is the number of snails present in unit volume of water, and

$k$  is constant representing the probability that one miracidium, liberated in unit volume of water in which there is a single snail, will succeed in penetrating it, or scanning power.

The influence of changes in the contamination rate can be readily derived from the expression. The inoculation rate varies directly with it. However, the influence of changes in snail density cannot be derived without some knowledge of the scanning power. At some initial densities it is great, at others small, but since the literature contains no traceable reference to measurement of scanning power we have no conception of even its order of magnitude and cannot therefore even guess the densities concerned.

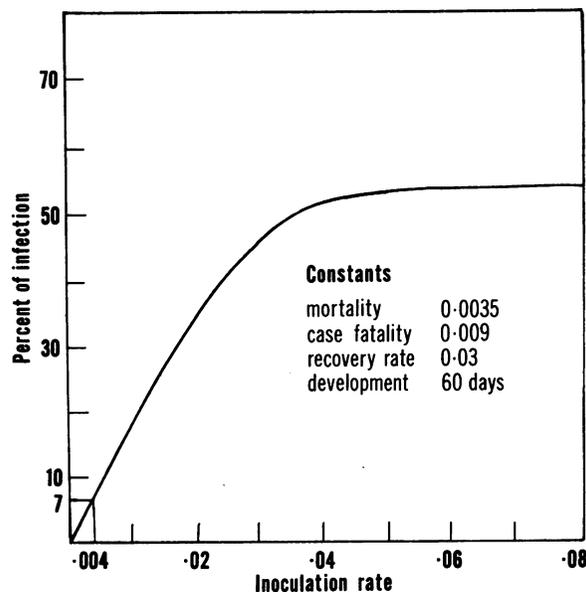
This equation is crucial in the dynamics of transmission of disease, and it might be said that the model had failed to throw light on the subject. This is not the case. The model does not fail; it represents the truth. The fact that we are completely ignorant of even the order of value of one of the constants involved is no fault of the model, which demonstrates the gap and

thereby indicates one line of study which would contribute to a knowledge of epidemiology.

Although a full understanding of the dynamics of schistosomiasis is blocked by weaknesses of understanding such as this, the subject can be pursued to a study of the relationships between the inoculation rate, as it is determined by the factors described above, and the resultant infection rate in snails. Two general types of relationship are to be expected, one in those conditions where the snail population undergoes seasonal regeneration, so that one age group will predominate at any time, and the other in conditions where the population remains undisturbed by seasonal factors and has an age distribution determined only by mortality rates. Allowance must be made for superinfection, for possible recovery from infection, and also for the fact that infection may sometimes prove lethal to the snail. This last has been suggested to have an important bearing on infection rates, and must therefore be taken into rigorous account in the model.

Expressions for these two relationships, which are very complicated owing to the need to take account of lethality continuing during infection, are given in the section "Mathematical Background," and the expression for the second type of condition is illustrated in figure 15. The constants used are derived from the

Figure 15. Trematode infection rates in snails



work of Pesigan and co-workers (13) and refer to *Schistosoma japonicum* infections in *Oncomelania quadrasi*. The infection rate would be expected to rise progressively with an increasing inoculation rate until saturation is reached, which with these constants would be at about 50 percent. The author's findings ranged from 0 to 6.97 percent. Even this highest value corresponds only to a daily inoculation rate of about 0.004, or once in 250 days.

This inoculation rate is extremely low, and since we know that it is directly related to the contamination rate, it is clear that changes in the contamination rate within a very broad range would have a direct effect on the snail infection rate. It is, however, far from clear what would be the effect of altering the numbers of snails short of eradicating them entirely. Reduction in their numbers would to some extent increase the inoculation rate, and hence the snail infection rate, but whether this would be proportional or not cannot be told till at least the order of the values of the constants shown to be important by mathematical models is known.

### Conclusion

I hope I have demonstrated the value of models in throwing light on epidemiology and in acting as guides to clarification of thought and to research.

These are only examples. In all vector-borne diseases there are comparable points of mystery and confusion which could be cleared up by the same approach—in Africa trypanosomiasis, in the difference between simian yellow fever in Africa and America, in leishmaniasis, and in a host of others.

I hope I have also shown the ways in which the biologist and the mathematician can come together to produce epidemiological models. This involves cooperation and a very strenuous effort at mutual understanding, as well as translation from biological to mathematical terms, and again from mathematical to biological terms, without which it is not complete.

But if mutual understanding is achieved, a proper study of the dynamics of transmission, which a model represents, can be a most valuable help to epidemiology.

## MATHEMATICAL BACKGROUND

### Malaria

The expressions used are quoted on the figures. A full statement of them is given in Macdonald (14).

### Schistosomiasis

#### Number of *Miracidia* in Water

The following symbols are used:

- $m$  Number of miracidia present in unit volume of water.
- $cdt$  Number of miracidia freshly liberated in unit volume of water in time  $dt$ .
- $adt$  Proportion of miracidia which die in time  $dt$ .
- $bdt$  Proportion of miracidia which would be immobilized and removed from circulation by contact with a snail in time  $dt$ , if there were one snail in unit volume of water.
- $s$  Number of snails in unit volume of water.

It is apparent that

$$\frac{dm}{dt} = c - m(a + bs) \quad [1]$$

whence, when conditions are static

$$m = \frac{c}{a + bs} \quad [2]$$

#### Inoculation Rate of Snails

$hdt$  Proportion of snails in which a new infection is established in time  $dt$ .

Other symbols as above.

By previous definition the number of miracidia present in unit volume of water is  $m$ , and the proportion making contact with a snail is  $bdt$ , whence

$$h = mb \quad [3]$$

The value of  $m$  given in [2] may be inserted here to give

$$h = \frac{cb}{a + bs} \quad [4]$$

It is, however, logical to modify this slightly to read

$$h = \frac{ck}{1 + ks} \quad [5]$$

where

$$k = a/b$$

which brings two natural partners together in the form of  $a/b$ , the reciprocal of the probability of a miracidium being removed from circulation by contact with a snail, during the whole of its natural life, if the density of snails were one in unit volume. This is termed the "scanning power."

### Infection Rate in Snails

The following additional symbols are required:

- $f$  Proportion of miracidium infections which kill the snail.
- $vdt$  Proportion of snails which die, through other causes than these infections, in time  $dt$ .
- $gdt$  Proportion which snails newly hatching in time  $dt$  bear to the total snail population.
- $rdt$  Proportion of affected snails which revert to the unaffected state in time  $dt$ .
- $n$  Period of time taken for development of an infection to maturity, with cercarial production.
- $x$  Proportion of snails with mature infections. The criterion of infection may be either discharge of cercariae or the detection of cercariae on examination after crushing, though the criterion of affected or unaffected, corresponding to  $r$  or the recovery rate, should be adjusted to coincide.
- $t$  Time.
- $p$  Probability of a snail surviving through 1 day.
- $e$  Base of natural logarithms.

It is known that superinfection occurs and it follows that the recovery rate,  $r$ , needs modification in the form described by Irwin in a paper by Macdonald (8), the effective rate being  $(r-h)$  when  $r > h$ , and 0 when  $r < h$ .

It is also known that infection is sometimes lethal to the snail, and it has been suggested that this may have a significant bearing on the infection rate among them, provision for which must be included in an analysis to allow examination of this type of belief, though it might

later be permissible to exclude it if it were shown to have an insignificant effect. Proper allowance for this involves also taking normal death and birth rates into account and, in consequence, the expressions developed are rather complicated in appearance. It should, however, be possible to use simplified forms for rough purposes when there is no desire to take possible minutiae into reckoning.

The line of argument developed by Ross (15), in his section V, applies perfectly to the analysis of the infection rate among snails of a given age. Following this, when  $h < r$ , let

$$\alpha = \frac{r+f}{2f} \quad [6]$$

$$\beta^2 = \alpha^2 - \frac{h}{f} \quad [7]$$

$$L = \alpha - \beta \quad [8]$$

$$L' = \alpha + \beta \quad [9]$$

Then the infection rate at any given age is given by

$$x_t = L \left[ 1 - \frac{L' - L}{L' e^{2f\beta t} - L} \right] \quad [10]$$

The infection rate in a community of snails, the age distribution of which is determined solely by a continuing death rate and birth rate not subject to seasonal or other such change, has been developed with the generous help of Dr. P. Armitage. The working has not yet been published, but it leads to the following expression

$$x = L \left[ e^{-(v+L)n} - \frac{v+Lf}{r+Lf-f} e^{-(r+Lr-n)n} \right] \quad [11]$$

which has been used in the preparation of figure 14. When  $h$  exceeds  $r$  it should be substituted for  $r$  in expressions 6 and 11.

### Arbovirus Infections

Arbovirus infection in the vertebrate is assumed to be followed, after an incubation period, by a short period of viremia, during which the individual may die, and then by a period of firm immunity in the survivors. The rates for death, emigration, and immigration are the

same for immune vertebrates as for nonimmune animals which do not contract the infection.

The notation used in the text in connection with malaria is followed, except that

$f$  is the proportion of infections which kill the vertebrate during the viremia stage.

$x$  is the proportion of animals which are immune.

$y$  is the proportion of animals with viremia.

$r$  is the probability of recovery from viremia in unit time.

$g$  is the proportion of animals newly born in unit time with respect to the total population.

The expression for mosquito life, and expectation, is the same as used in the statement of malaria, as is also the reproduction rate,  $z$ , bearing in mind that the recovery rate,  $r$ , refers to the probability of recovery from viremia.

The mosquito infection rate is given by

$$s = \frac{p^n ay}{ay - \log_e p} \quad [12]$$

The working of these expressions, which is complicated, is not here stated, but it leads to a definition of the final state, when stability is reached and rates are no longer increasing, though free interplay between the two infection rates has occurred. The value of  $x$ , the proportion of the population which is immune, is found by solving a quadratic equation, to do which let

$$\gamma = \frac{(1-f)^2}{f} + \frac{ag}{2rzf(-\log_e p)} \quad [13]$$

and

$$\delta^2 = \gamma^2 + \frac{(1-f)(z-1)}{fz} \quad [14]$$

when the required limits are given by

$$L_x = -\gamma + \delta \quad [15]$$

$$L_y = \frac{gL_x}{r(1-f)(1-f+fL_x)} \quad [16]$$

$$L_s = \frac{p^n L_y}{aL_y - \log_e p} \quad [17]$$

The possibility of maintenance of this endemic state depends on the size of the population, its birth rate, the duration of viremia and the case fatality associated with infection. The critical values of these may be roughly estimated by noting that transmission becomes progressively decreased when the value of  $y$  is such that it indicates a fractional number.

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