SELECTIVE HOST MORTALITY IN A CATALYTIC MODEL APPLIED TO SCHISTOSOMIASIS

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The two-stage catalytic model of the prevalence of disease in a population gives estimates of rates that are epidemiologically important. My purpose here is to examine the effects on those rates of correcting one implicit but false assumption of the model. This examination and its application to schistosomiasis illustrate how successive approximations to reality can improve mathematical models which remain inevitably approximate.

The implicit assumption of the model to be corrected is that the death rate of individuals infected with the disease does not differ from that of individuals never infected. In the early applications to yaws and histoplasmosis, Muench (1959, p. 63, 67) noted that excess mortality of infected individuals made it necessary to interpret estimated values of the rate of exit from the state of being infected as something more than simply the rate of loss of infection. He did not show how to calculate the impact of selective host mortality on the estimates. Subsequent applications of the model to schistosomiasis have neglected Muench's warning or overstated the role of selective host mortality. The following analysis applies to any disease for which this model has been used, and may be even more important for some viral and bacterial diseases than for schistosomiasis.

Mathematical analysis of the ecology, epidemiology, and evolution of schistosomiasis is burgeoning. Efforts since 1960 include Cohen (1970), Goffman and Warren (1970), Hairston (1962, 1965*a*, 1965*b*), Jobin and Michelson (1967), Leyton (1968), Linhart (1968), Macdonald (1965), Tallis and Leyton (1966, 1969), and Nåsell and Hirsch (1971).

Assumptions of existing models vary enormously. Hairston's (1965*b*) and my (1970) efforts covertly assume constant death rates. Goffman and Warren (1970) assume mortality depending on the state of infection. The scope of application of the models also varies. Jobin and Michelson (1967) focus exclusively on snail populations. Hairston (1962) and Goffman and Warren (1970) attempt to encompass the entire ecology of the disease.

The resulting tangle of notations, assumptions, and conclusions may appear forbidding to a fieldworker in search of enlightenment, but is not less forbidding than the chaos of epidemiological data from scattered field sites, parasites, snails, and mammalian hosts. Cure of this confusion requires more critical and more cooperative scrutiny of the assumptions, methods, and goals of both modelers and fieldworkers.

A MODIFIED CATALYTIC MODEL FOR SCHISTOSOMIASIS

Muench (1959, p. 54–56) proposed and Hairston (1965*b*) applied to human schistosomiasis a simple mathematical model intended to account for the age-prevalence curve in a population in terms of a force of infection and a force of defection (loss of evidence of current infection). Let $u(t)$ be the fraction of the population of age t which is not now and has never been infected. Let $y(t)$ be the fraction of the population of age t which is infected, and let $z(t)$ be the fraction of the population of age t which was previously infected but which no longer gives current evidence of being infected. The force of infection a is the fraction of previously uninfected individuals who become infected per unit of time (per year, for example); the force of defection b is the fraction of currently infected individuals who lose all signs of infection per unit of time. Then the two-stage catalytic model is:

$$\begin{aligned} du/dt &= -au, & u(0) &= 1; \\ dy/dt &= au - by, & y(0) &= 0; \\ dz/dt &= by, & z(0) &= 0. \end{aligned} \tag{1}$$

The solution for $y(t)$ is supposed to describe the observed fraction of individuals aged t who are infected.

Now suppose that m is the crude rate of mortality (the fraction of individuals dying per year) among individuals who show no current evidence of infection: those never infected $u(t)$ plus those who have lost infection $z(t)$. Suppose the crude rate of mortality among those $y(t)$ currently infected is $m + \varepsilon$. (Clearly, as N. G. Hairston [personal communication] has pointed out, it is more plausible to assume a mortality $m + \varepsilon'$ for those previously infected which differs from the mortality m of those never infected. But no available data permit this difference ε' to be estimated for schistosomiasis, so we set it aside for the present.) Let $s(t)$ be the fraction of those born who survive to age t, $s = u + y + z$. Then Muench's catalytic model (1) is a special case of the slightly more general model:

$$\begin{aligned} du/dt &= -au - mu, & u(0) &= 1; \\ dy/dt &= au - by - (m + \varepsilon)y, & y(0) &= 0; \\ dz/dt &= by - mz, & z(0) &= 0; \\ ds/dt &= -m(u + y + z) - \varepsilon y, & s(0) &= 1. \end{aligned} \tag{2}$$

It follows from a general theorem (Cohen 1973) that if $\varepsilon = 0$, the infected fraction of the living population y/s at any age predicted by model (2) is indistinguishable from the infected fraction y of the living population predicted by model (1). However, if infection affects mortality, so that $\varepsilon \neq 0$, then according to model (2),

$$\frac{y}{s} = \frac{(b + \varepsilon)\, a(e^{-at} - e^{-(b+\varepsilon)t})}{(b + \varepsilon)\varepsilon e^{-at} - a\varepsilon e^{-(b+\varepsilon)t} + b(b - a + \varepsilon)}. \tag{3}$$

Before I continue with the analysis of the extended model (2), it is use-

ful to point out some of its assumptions and remaining possible shortcomings. Model (2) shares with Muench's (1959) original model (1) the assumptions (Sturrock and Webbe 1971) that the ages of individuals can be determined, that all (or a fixed fraction, Hairston's [1965*b*] application) of them are exposed to infection, that the forces of infection and loss of infection are constant for any particular population, and that infections are observable. Both models further assume that once an individual loses infection, he runs no risk of reinfection; this assumption is particularly implausible for schistosomiasis, though perhaps not for viral or bacterial diseases which cause different kinds of immune responses. Both models assume that all forces (of infection, defection, mortality, and emigration) may be described as if they operate linearly on the populations at risk. Thus both models assume, for example, that when a fixed fraction of the population has never been infected, the number of individuals who become infected in the next short interval of time is independent of the number of individuals currently infected. While model (1) neglects both migration and mortality, model (2) can incorporate emigration in the term for mortality. Model (2) assumes that the age-specific rate of mortality (plus emigration) is constant over age. Several of these assumptions offer clear opportunities for further rapprochement of the model with reality.

Muench's method of estimating the parameters in (1), which is the method adopted in the applications of this model below, depends on the area under the age-prevalence curve. For the modified model (2), if d is the highest age considered, the area under the age-prevalence curve $y(t)/s(t)$ is

$$\begin{aligned} A(a, b, \varepsilon) &= \int_0^d (y/s)\,dt \\ &= \frac{1}{\varepsilon} \ln \frac{(b+\varepsilon)\,(b-a+\varepsilon)}{(b+\varepsilon)\varepsilon e^{-ad} - a\varepsilon e^{-(b+\varepsilon)d} + b(b-a+\varepsilon)}. \end{aligned} \tag{4}$$

In the limit as ε approaches zero, by l'Hôpital's rule, $A(a, b, \varepsilon)$ approaches

$$A(a, b, 0) = \frac{b(1-e^{-ad}) - a(1-e^{-bd})}{b(b-a)}, \tag{5}$$

which is precisely

$$\int_0^d y\,dt$$

where y is defined by model (1) without mortality.

When the maximum age observed, d, is so large that e^{-bd} and e^{-ad} are both much smaller than one, the integral (4) in the model with mortality approaches

$$A_\infty(b, \varepsilon) = \frac{1}{\varepsilon} \ln \frac{b+\varepsilon}{b}. \tag{6}$$

The corresponding integral (5) in the absence of mortality becomes the limit as ε approaches zero,

$$A_\infty(b, 0) = 1/b, \tag{7}$$

which is just the average time during which an (immortal) individual shows the infection.

In (6) and (7) the subscript ∞ indicates that d is taken as very large. In both cases, when sufficiently large ages are included, the area under the age-prevalence curve is independent of the force of infection a because every surviving individual becomes infected.

To estimate the force of infection a and the force of defection b by Muench's method of moments, the area under an observed age-prevalence curve, standardized so that the highest age observed equals d, is calculated. Since I now consider the possibility that infection may affect the death rate as described by (2), I call this calculated area $\hat{A}(a, b, \varepsilon)$. In applications so far this area is set equal to $A(a, b, 0)$ on the assumption that there is no increment in mortality due to infection. Similarly, the mean age $\bar{t}$ of the infected population is set equal to the mean age

$$\int_0^d tydt \Big/ \int_0^d ydt$$

calculated from (1). Muench's nomogram (1959, p. 99) solves these two equations for estimates $\hat{a}$ and $\hat{b}$ of a and b. Henceforth I ignore the role of $\bar{t}$ and concentrate on $\hat{A}$.

Obviously the estimates obtained in this way are not correct except when $\varepsilon = 0$. The following calculations show how to correct separately the estimates $\hat{a}$ and $\hat{b}$ obtained from Muench when ε is known approximately and is small.

For any ε, let $a(\varepsilon)$ be the force of infection which gives the same total area under the age-prevalence curve as $\hat{a}$, $\hat{b}$, and $\varepsilon = 0$; and similarly for $b(\varepsilon)$. Thus, $a(\varepsilon)$ and $b(\varepsilon)$ satisfy

$$A[a(\varepsilon), \hat{b}, \varepsilon] = A[\hat{a}, b(\varepsilon), \varepsilon] = A(\hat{a}, \hat{b}, 0). \tag{8}$$

If ε is not too large, then $a(\varepsilon)$ and $b(\varepsilon)$ may be closely approximated by the first terms of a Taylor series expansion around $\hat{a}$ and $\hat{b}$ as

$$\begin{aligned} a(\varepsilon) &= \hat{a} + \varepsilon \left(\frac{\partial a}{\partial \varepsilon} \right)_{\epsilon=0}, \\ b(\varepsilon) &= \hat{b} + \varepsilon \left(\frac{\partial b}{\partial \varepsilon} \right)_{\epsilon=0}; \end{aligned} \tag{9}$$

and the partial derivatives in (9) may be found by application of the implicit function theorem to (8):

$$\begin{aligned} \frac{\partial a}{\partial \varepsilon} &= - \frac{\partial A}{\partial \varepsilon} \Big/ \frac{\partial A}{\partial a}, \\ \frac{\partial b}{\partial \varepsilon} &= - \frac{\partial A}{\partial \varepsilon} \Big/ \frac{\partial A}{\partial b}. \end{aligned} \tag{10}$$

The partial derivatives on the right of (10) at $\varepsilon = 0$ may be found from (4) and (5) to be the following unattractive expressions:

$$\left(\frac{\partial A}{\partial \varepsilon}\right)_{\epsilon=0} = \frac{1}{2}\left[\frac{-b^2 - (b-a)^2}{b^2(b-a)^2} - \frac{2(e^{-ad} + ade^{-bd})}{b(b-a)} + \frac{(be^{-ad} + b - ae^{-bd})^2}{b^2(b-a)^2}\right]; \tag{11}$$

$$\left(\frac{\partial A}{\partial a}\right)_{\epsilon=0} = \frac{e^{-bd} + bde^{-ad} - 1}{b(b-a)} + \frac{ae^{-bd} - be^{-ad} + b - a}{b(b-a)^2}; \tag{12}$$

$$\left(\frac{\partial A}{\partial b}\right)_{\epsilon=0} = \frac{1 - e^{-ad} - ade^{-bd}}{b(b-a)} + \frac{(2b-a)(be^{-ad} - ae^{-bd} + a - b)}{b^2(b-a)^2}. \tag{13}$$

Thus, given d and ε, to find the corrected forces $a(\varepsilon)$ and $b(\varepsilon)$ of infection and defection, first calculate the area under the age-prevalence curve, find the estimates $\hat{a}$ and $\hat{b}$ from Muench's nomogram, and substitute into (11), (12), and (13), then into (10), and finally into (9).

When d is very large, applying (10) and (9) to the parameter b in (6) and (7) gives

$$\left(\frac{\partial A}{\partial \varepsilon}\right)_{\epsilon=0} = -\frac{1}{2b^2}, \left(\frac{\partial A}{\partial b}\right)_{\epsilon=0} = -\frac{1}{b^2} \qquad (d = \infty),$$

which also follow directly from (11) and (13), and finally

$$b(\varepsilon) = \hat{b} - \varepsilon/2. \tag{14}$$

The conclusions from this calculation are that, when e^{-ad} and e^{-bd} are small compared with one, if infection with the disease contributes an increment to mortality, then the value for the rate of loss of infection obtained for model (1) by Muench's methods overestimates by half that increment the rate of loss of infection in model (2) which allows for differential mortality. When e^{-bd} and e^{-ad} are nonnegligible, the estimated rates $\hat{a}$ and $\hat{b}$ of gain and loss of infection can be corrected by the steps following (13). Both corrected rates $a(\varepsilon)$ and $b(\varepsilon)$ are sufficient separately to adjust the area under the age-prevalence curve so that (8) is satisfied. Hence application of both corrections simultaneously would overadjust. The actual value of a must lie between $\hat{a}$ and $a(\varepsilon)$, and the actual value of b must lie between $\hat{b}$ and $b(\varepsilon)$. For infinite d only $\hat{b}$ requires correction. Hence the larger d is, the closer a will lie to $\hat{a}$ and the closer b will lie to $b(\varepsilon)$.

OBSERVED MORTALITY AND CORRECTED ESTIMATES FOR HUMANS

I now examine what impact infection with the adult stages of schistosomes may have on humans. In the next section I examine what impact infection with the larval stages may have on one species of snail.

The prevalence of infection with schistosomes in a population of living humans is determined by parasitological examinations of samples of urine and feces. This measure of prevalence allots to the defected fraction z of the population those individuals, not shedding eggs, who may still harbor schistosomes or who may suffer from damage to the liver, spleen, kidney, bladder, or other organs.

Both N. G. Hairston (personal communication) and D. J. Bradley (personal communication) have pointed out that such defected individuals may well suffer a greater risk of death than those never infected. Hence if ε is estimated as the difference in mortality between the fraction y of the population currently infected and the average mortality in the fractions $u + z$ not currently showing infection, this difference understates the true excess mortality among those who have ever been infected with schistosomiasis.

Since no epidemiological studies appear to have measured the difference in mortality between individuals in the never infected fraction u of the population and individuals in the defected fraction z of the population, for the present it is necessary to estimate m as the average death rate of all individuals not presently shedding eggs, whether before or after infection, and ε as the increase in death rate of all individuals currently shedding eggs.

The only useful study of the effect of schistosomiasis on human mortality known to me is by Forsyth (1969). In a 2-year study in Zanzibar, Forsyth found 65% of a population of approximately 1,000 infected with *Schistosoma haematobium* before control measures were attempted, 45% infected after. Hence the prevalence of infection is approximately 50% over both years. Forsyth attributed four deaths during the 2 years to schistosomiasis. Assuming these deaths occurred to people assayed as currently infected gives an estimate of $\varepsilon = 0.004$ per year. If the remaining 18 deaths observed during this period in the population were unrelated to schistosomiasis, m is estimated as 0.009 per year. Hence infected individuals have a nearly 50% greater chance of death per year than do currently uninfected individuals.

The margin of uncertainty around these estimates is very great, since Forsyth did no autopsies to demonstrate the presence of eggs or adult worms in individuals whose deaths he attributed to schistosomiasis or in the other individuals. Edington (1957) examined the bladder or ureter histologically "in all autopsies in which disease of the genito-urinary system was the primary cause of death" and found schistosomiasis "to be directly responsible for the resulting pathological condition" in only nine out of 24. Hence the schistosomal death rate based on Forsyth's data may well be too high. The rate may also be too low because the 66 people who left the area during his initial survey would be especially likely to be young adult males, those people at peak risk of death from the disease. But to admit that the data are less than ideal is not to render them worthless, and for the present they are superior to any other available information.

Walker, Walker, and Richardson (1970) reported that *S. haematobium,* prevalent in 62.5%, and *Schistosoma mansoni,* prevalent in 58.5% of Bantu school children in a village in South Africa were "not associated with detectable disabilities in relation to growth, physical activity or intelligence."

This surprising finding is not inconsistent with Forsyth's (1969) conclusion that "urinary schistosomiasis in Zanzibar is not a chronic debilitating disease nor is it primarily important as a cause of morbidity but rather because it causes deaths among persons apparently in good health."

The initial and still sole application of Muench's catalytic model (1) to the age-prevalence distributions of human schistosomiasis is due to Hairston (1965*b*). Because the catalytic model (1) did not describe the age-prevalence curve of the population as a whole, Hairston modified the original model in two ways. First, he fitted the age-prevalence distribution of children under 5 years old separately from the age-prevalence distribution of the older population. Second, observing that a certain fraction of the older population appeared to be permanently infected, he assumed that the processes of infection and defection in the catalytic model occurred only among the complementary fraction of the population.

From the age-prevalence distribution of *S. haematobium* in Syria, Hairston (1965*b*) estimated that 7.5% of the population aged 5 and older appeared never to lose their infections. For the remaining population he estimated $\hat{a} = 0.125$ and $\hat{b} = 0.35$, based only on the age-prevalence data from 5 to 14 years. Hence in his procedure $d = 14 - 5 + 1 = 10$ years. The exponential term $e^{-ad} = e^{-1.25}$ cannot be neglected. So it is necessary to follow the procedure after (13).

From the age-prevalence distribution of *S. haematobium* in parts of an Egyptian control project, ignoring the concomitant presence of *S. mansoni*, Hairston estimated that 25% of the population aged 5 and older appeared never to lose their infections. For the remaining population he estimated $\hat{a} = 0.30$ and $\hat{b} = 0.10$. Since again $d = 10$, the term $e^{-bd} = e^{-1}$ cannot be neglected.

If we make the dubious assumption that the mortality due to *S. haematobium* which Forsyth (1969) found in Zanzibar in the absence of *S. mansoni* is relevant to Hairston's study sites, and recalculate ε based on Forsyth's population 6 years old or older, we still obtain $\varepsilon = 0.004$.

Then for Syria, equation (9) gives the corrected estimates $a(0.004) = 0.12604$, $b(0.004) = 0.34760$. For Egypt, equation (9) gives $a(0.004) = 0.30351$, $b(0.004) = 0.09880$. These and the analogous results for snails are summarized in table 1, along with the age range d of individuals on which the original estimates are based, and the fraction k of the population permanently infected. As a numerical indication of how well the linear approximations (9) satisfy the equalities (8), the last two columns of table 1 give the absolute values of the relative differences

$$\{A[a(\varepsilon), \hat{b}, \varepsilon] - A(\hat{a}, \hat{b}, 0)\}/A(\hat{a}, \hat{b}, 0) = \delta(a)$$

and

$$\{A[\hat{a}, b(\varepsilon), \varepsilon] - A(\hat{a}, \hat{b}, 0)\}/A(\hat{a}, \hat{b}, 0) = \delta(b).$$

The linear approximations are clearly better when the increment in mortality ε is small relative to the estimated rates $\hat{a}$, $\hat{b}$, as in the human cases, than when ε is relatively large. The error in keeping the area constant is never worse than 1%.

TABLE 1

ORIGINAL AND ADJUSTED ESTIMATES OF RATES OF INFECTION AND DEFECTION IN THE TWO-STAGE CATALYTIC MODEL, IN TWO SAMPLES OF HUMAN AND FIVE SAMPLES OF SNAIL POPULATIONS EXPOSED TO SCHISTOSOMIASIS

Host	*Schistosoma*	Locale	Time Unit
Humans	*haematobium*	Syria	Year
Humans	*haematobium*	Egypt	Year
Biomphalaria glabrata:			
Sample 4	*mansoni*	Saint Lucia	Week
Sample 5	*mansoni*	Saint Lucia	Week
Sample 6	*mansoni*	Saint Lucia	Week
Sample 7	*mansoni*	Saint Lucia	Week
Sample 8	*mansoni*	Saint Lucia	Week

NOTE.—Symbols are explained in the text.

In the two human cases, if one takes $\hat{a}$ as correct and assigns all the error to $\hat{b}$, the correction to $\hat{b}$ is still less than 0.003 for Syria and less than 0.002 for Egypt. Hairston gives his estimates to only two decimal places, so he apparently does not claim accuracy to within 0.003 per year, which is the largest correction required by assuming that Zanzibar's schistosomal mortality prevails in Syria and Egypt. The only caveat which should be attached to his results is that he has not measured the bias in his estimates due to mortality in his study areas. The effect of that bias is systematically to exaggerate the force of defection and to underestimate the force of infection.

Partial confirmation of this conclusion comes from the same study area in Egypt (Farooq and Hairston 1966). Children 5 and 6 years old observed at the beginning and end of 1 year showed a rate of loss of infection with *S. haematobium* of 0.049 per year. This "true" value of b (for those ages) is just half the rate $\hat{b} = 0.10$ estimated (for all ages) from the catalytic model.

D. J. Bradley (personal communication) pointed out that these same calculations may be viewed in an opposite sense: if the estimate of ε found in Zanzibar is typical of the increment in mortality caused by *S. haematobium* generally, and if the parameter values obtained from fitting a catalytic model (1) are typically of the size that Hairston found in Egypt and Syria, then unless one seeks estimates of rates accurate to less than 0.01 per year, one need not worry about correcting for differential mortality of infected hosts. With other diseases, or markedly different increments in mortality and markedly different rates of infection and defection, the steps following (13) show how to calculate whether differential host mortality may lead to biases which are important at the level of accuracy desired.

OBSERVED MORTALITY AND CORRECTED ESTIMATES FOR SNAILS (*Biomphalaria glabrata*)

Sturrock and Webbe (1971) recently applied Muench's model (1) to age-prevalence data on three species of snails collected from the field. Snails

TABLE 1 (*Continued*)

$\hat{a}$	$a(\varepsilon)$	$\hat{b}$	$b(\varepsilon)$	ε	d	k	$\lvert\delta(a)\rvert$	$\lvert\delta(b)\rvert$
0.125	0.1260	0.35	0.3476	0.004	10	0.075	8×10^{-6}	1×10^{-6}
0.300	0.3035	0.10	0.0988	0.004	10	0.250	2×10^{-5}	2×10^{-5}
0.040	0.0487	0.422	0.3387	0.1087	15	0	3×10^{-3}	7×10^{-4}
0.070	0.0906	0.296	0.2254	0.1087	15	0	1×10^{-2}	3×10^{-3}
0.028	0.0320	0.704	0.6142	0.1087	15	0	6×10^{-4}	2×10^{-4}
0.040	0.0458	0.700	0.6161	0.1087	15	0	1×10^{-3}	3×10^{-4}
0.025	0.0340	0.151	0.0624	0.1087	15	0	1×10^{-2}	1×10^{-3}

were classified by size. Ages were imputed from field growth curves which, for the species considered here, *Biomphalaria glabrata* (= *Australorbis glabratus*), are as yet unpublished. For four of five samples of *B. glabrata* collected in Saint Lucia, West Indies, on consecutive fortnights (numbered samples 4–8 in Sturrock and Webbe [1971] and in our table 1), the model (1) with no mortality fitted the observed age-prevalence curves acceptably according to Pearson's χ^2 criterion of goodness of fit. (Even if the number of degrees of freedom in Sturrock and Webbe's [1971] table 2 is reduced by two to take account of the two free parameters a and b, four of the five fits are still acceptable at the 1% level.) The resulting estimates $\hat{a}$ and $\hat{b}$ of the rates of infection with *Schistosoma mansoni* and defection appear in table 1.

Data of Pan (1965) describe the impact of infection by *S. mansoni* on the survival of *B. glabrata* in the laboratory. These results cannot be applied uncritically in the field, but at the moment they provide more information than any other source. Pan exposed one group of 150 "adolescent" (small, not laying eggs) snails to infection with *S. mansoni*. Pan established another group of 100 snails matched for initial size and maturity under the same conditions without exposure to infection.

Richards (1970) has shown that several genetic factors determine susceptibility of *Biomphalaria glabrata* to infection with *S. mansoni*. Some individuals appear to be refractory to infection throughout life, others to become refractory at sexual maturity. The frequency of the refractory genotypes among the snails Pan (1965) exposed is unknown, as is the frequency in any natural population of these snails. Hence any application to the field of mortality estimates obtained in the laboratory is subject to revision when estimates of the frequencies of the refractory genotypes become available.

Model (1) assumes that the age-specific mortality of infected and uninfected snails would be constant at all ages and the same in both groups, so that if the logarithm of the number of survivors in each group were plotted against time, the two groups would fall along parallel lines with slopes equal to $-m$. Model (2) leads to the expectation that log (uninfected survivors) would fall along a straight line with slope $-m$ while log (infected survivors)

would fall along a straight line with slope $-(m + \varepsilon)$. The logarithms of the numbers of survivors in each of Pan's groups are plotted in figure 1, starting from the fifth week postinfection. Snails exposed to infection first began shedding cercariae in that week. Along with the points based on Pan's data are straight lines fitted by least squares to the logarithms.

Clearly model (2) approximates the data better than model (1), though model (2) also is not perfect. The estimate of ε obtained by taking the difference between the slopes of the two lines is $0.1157 - 0.0070 = 0.1087$. This value is the risk of mortality per week attributable to infection with *S. mansoni,* on the assumption that all snails in the exposed group actually became infected and remained so. If not all exposed snails acquired and retained infections, then ε is even larger than 0.1087.

Pan (1965) also divided the sexually mature unexposed snails who survived this first experiment into two groups and exposed one group to infection with *S. mansoni.* A quick and approximate analysis of the results indicates that the difference in mortality, attributable to exposure to infection, is even larger in older snails than in "adolescent" snails.

Sturrock and Sturrock (1970) also observed the impact of infection with *S. mansoni* on *B. glabrata* in laboratory-reared snails hatched from eggs of adult snails freshly caught in Saint Lucia. But attempting the kind of analysis shown in figure 1 with their data is perilous for three reasons. First, they give the length of the prepatent period only as ranging from 3 to 5 weeks, without specifying its exact length for each exposed group. Second, the percentages surviving must be estimated by eye from their graphs,

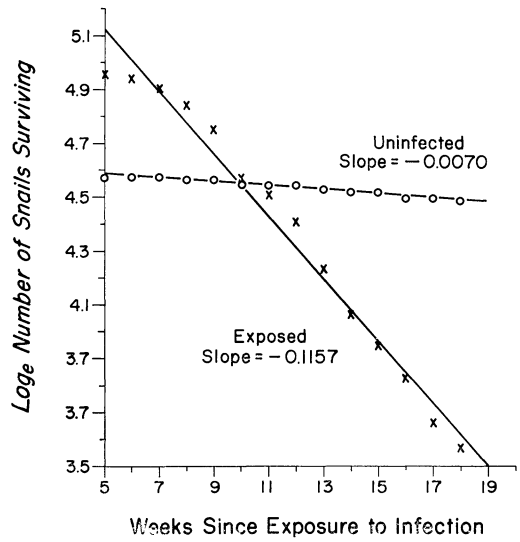

FIG. 1.—Natural logarithms of the numbers of survivors in a group of snails exposed to *Schistosoma mansoni* and in an unexposed group, based on data of Pan (1965), and fitted straight lines; starting from first week when snails shed cercariae.

whereas Pan (1965) tabulates actual numbers surviving. Because the number of infected snails who survived to the end of the prepatent period cannot be derived from the information given by Sturrock and Sturrock (1970), these percentages cannot be reconverted into absolute numbers of snails surviving. Third, because each exposure and control group of Sturrock and Sturrock (1970) had only 20 snails, the sampling variability of the estimated forces of mortality is substantially greater.

If these difficulties are circumvented by assuming a fixed prepatent period of 5 weeks, using the estimated percentages instead of actual numbers, and ignoring sample size, then according to the data of Sturrock and Sturrock (1970), the estimated increment in mortality due to infection is of the same order of magnitude as that estimated from Pan (1965). Once again, the older the snails when infected, the greater the apparent increment in mortality due to infection. Since the average age of snails in the field when infected appears to be totally unknown, the average increment in mortality due to infection can only be estimated as lying somewhere in the observed range of increments.

If $\varepsilon = 0.1087$ is taken as the best estimate of the increase in mortality of *B. glabrata* due to schistosomal infection, then the approximate calculations described after equation (13) lead to the revised estimates $a(\varepsilon)$ and $b(\varepsilon)$ in table 1. These revisions could increase the estimate of a by as much as 36% (from 0.025 to 0.0340 in sample 8) and could decrease the estimate of b by as much as 59% (from 0.151 to 0.0624 in sample 8). In sample 5, which fit model (1) best according to the χ^2 criterion, taking account of differential mortality could increase the estimate of a by 29% and could decrease the estimate of b by 24%.

The changes in the shape of the predicted age-prevalence curve (3) caused by adjusting $\hat{a}$ and $\hat{b}$ separately while keeping the area under the curve constant are shown for sample 5 in figure 2, along with the original data of Sturrock and Webbe (1971) and the age-prevalence curve predicted by model (1). (For weeks 8–9.5, in the sample of 550 snails, the number of infected snails reported by Sturrock and Webbe [1971] in their figure 2 has been changed from 34 to 84 in order to make the calculated proportion infected consistent with that shown in their histogram.) When $\hat{a}$ is adjusted to $a(\varepsilon)$, holding area constant, predicted prevalence is higher over the younger ages, and lower over the older ages, than when differential mortality is ignored. On the contrary, when $\hat{b}$ is adjusted to $b(\varepsilon)$, holding area constant, predicted prevalence is lower over the younger ages, and higher over the older ages, than when differential mortality is ignored. This same pattern of change in the expected age-prevalence curve holds for all seven cases, snails and humans, in table 1, and can be shown mathematically to hold in general. Hence, though the size of sample 5 is probably too small to permit reliable discrimination between the three predicted age-prevalence curves in figure 1, a sufficiently large sample size could show whether the observed age-prevalence curve is best described by correcting the force of infection, or the force of defection, or both, for the effects of differential mortality.

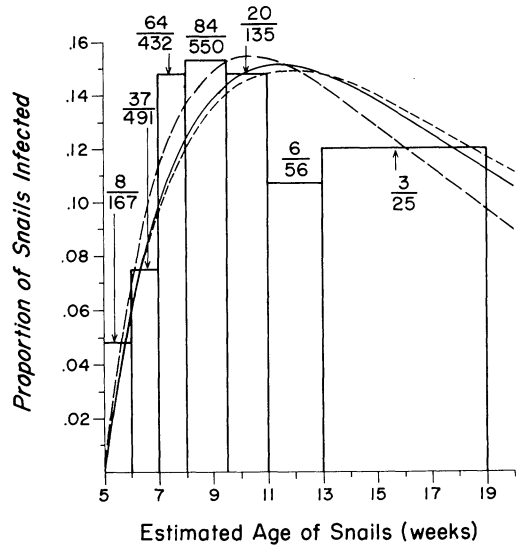

FIG. 2.—Observed age-prevalence distribution in sample 5 of *Biomphalaria glabrata* in Saint Lucia, according to Sturrock and Webbe (1971), starting from first week when snails shed cercariae; and three predicted age-prevalence curves having the same area beneath them: solid curve = original two-stage catalytic model; long dashes = force of infection adjusted for differential mortality; short dashes = force of defection adjusted for differential mortality.

Neither Pan's (1965) estimated weekly mortality for infected snails (0.1157 according to the slope of the solid line fitted in fig. 1) nor Sturrock and Webbe's "average overall weekly mortality of 141 per 1,000 field snails over the period sampled" (1971) in samples 4–8 is sufficient to account completely even for the lowest $\hat{b}$ in table 1 (although both of these estimates of mortality exceed the estimated $\hat{b}$ for sample 3 of *B. glabrata* in Sturrock and Webbe [1971]). Hence it seems excessive to ignore the possibility of loss of apparent infection (cessation of shedding) and to attribute the entire force of defection to selective host mortality, as do Sturrock and Webbe (1971): "differential mortality between infected and uninfected snails rather than the development of immunity is a more reasonable interpretation of the force of loss of infection which can therefore be expressed as the number of deaths per 1,000 infected snails per week."

What can be concluded with confidence is that when infection changes mortality, estimates of the rates of infection and defection risk being in error if they ignore such a change. When the differential mortality due to infection is substantial, the characteristic patterns of change in the predicted age-prevalence curve that follows from correcting for the bias in the force of infection and for the bias in the force of defection (illustrated for sample 5 of *B. glabrata* in fig. 2) open the possibility of determining empirically where the error lies.

SUMMARY

Analysis of a "catalytic" model used to study schistosomiasis and other diseases shows that if apparent infection with the disease contributes an increment to mortality, then a standard method for finding the force of infection and the force of defection (loss of infection) gives biased estimates. Under plausible approximations, the force of defection obtained by the standard method overestimates the true rate of loss of infection by half the increment in mortality due to infection.

Evidence from the literature that infection with schistosomes does increase human mortality suggests an upward bias in published estimates of the rate of loss of infection. This suggestion is confirmed in one instance by a subsequent direct measurement showing that the true rate of loss of infection is lower than that previously estimated. Published estimates of the rates of infection and defection among snails are substantially biased by mortality due to infection. Increased awareness of the impact of differences in mortality between infected and uninfected individuals should forestall uncritical acceptance of estimates of incidence and loss of infection obtained from methods which ignore these differences.

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