Ann. Rev. Ecol. Syst. 1977. 8:209–33
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MATHEMATICAL MODELS OF SCHISTOSOMIASIS

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INTRODUCTION

Human schistosomiasis (or synonymously, bilharzia) is a family of diseases caused primarily by three species of the genus *Schistosoma* of flatworms. The adult worms inhabit the blood vessels lining either the bladder or intestine, depending on the species of worm. The worms are also known as blood flukes.

The worldwide prevalence of schistosomal infections has not been measured credibly. A figure conventionally cited is 200 million people, or one of every 20 people on the planet. Except for imported cases, the disease is virtually unknown in the rich countries of the world.

"There is little doubt that all three schistosomes can cause considerable pathological change, sometimes in a comparatively large proportion of the population, but the evidence suggests that only a proportion of those so affected die of the disease" (29, p. 168). The absence of quantitative information from this assessment of the impact of the infection on health fairly reflects the information available.

Jordan & Webbe (29) review human schistosomiasis. Malek (40) and Hairston (24) emphasize the ecological point of view. Warren & Newill (59) cite 10,286 references. Some material here is drawn from Cohen (11) and Fine (18).

After sketching the life cycle of *Schistosoma mansoni,* this chapter reviews mathematical models of schistosomiasis. The bibliography of published works aspires to completeness through 1976.

LIFE CYCLE OF SCHISTOSOMIASIS

The life cycle of the three major human schistosome species (Figure 1) consists of an obligatory alternation of sexual and asexual generations. The sexual generation occurs in man (and sometimes other mammals). The asexual generation must pass through specific snails. The quantitative estimates in the following refer chiefly to *S. mansoni.*

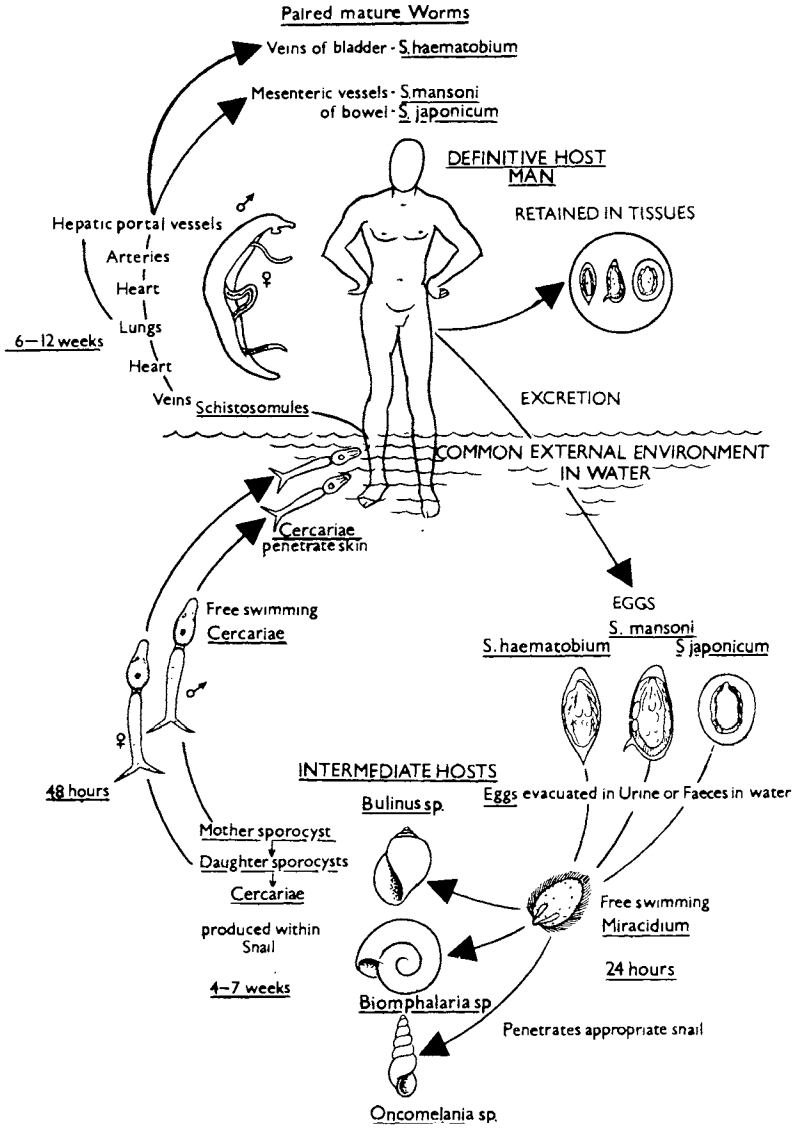

Figure 1 The life cycle. [From (29), p. 7. Courtesy of the authors and Charles C Thomas, publisher.]

Eggs produced by the sexual stage leave people via urine (in the case of *S. haematobium*) or feces (*S. mansoni* and *S. japonicum*). Eggs that reach water shed their shells and hatch a ciliated free-swimming stage called a miracidium.

A miracidium that locates a snail within approximately one day penetrates it. If the snail is of the appropriate species and genotype, the miracidium multiplies asexually through two larval stages into thousands of cercariae.

Each cercaria that escapes from the snail, starting 4–5 weeks after the initial infection (6 weeks in *S. japonicum*), lives approximately 2 days. It swims until it encounters a skin of suitable warmth and smell. When one of the human schistosomal cercariae enters human skin, it becomes a wormlike "schistosomule."

A schistosomule of *S. mansoni* migrates to the lung, sometimes producing a cough, then appears in the portal system of the liver where it reaches sexual maturity and mates. Worm pairs then migrate to the blood vessels lining the lower small intestine and the large intestine.

At this point the couple of worms resemble a hot dog in a roll. The female, 7–17 mm long, lies in the gynecophoric canal of the male, who is 6–13 mm long and cylindrically shaped to correspond to the walls of their home, a blood vessel. The forward third of the female's body is devoted to the uterus, which contains one to two eggs at a time. The female is estimated to lay from 100 to 300 eggs a day.

Some of these eggs work through the wall of the blood vessel into the lumen of the intestine. Carried by feces, these eggs again begin the life cycle. The interval from the entry of cercariae into human skin to the first detectable passage of eggs in the feces can vary from 4 weeks for *S. japonicum* to 5 or 6 weeks for *S. mansoni* and 13 weeks for *S. haematobium.*

Apart from an occasional aberrant worm that wanders into the wrong organ, such as the brain or eye, most of the disease caused by the infection results from the eggs that do not escape with feces. Some of these get stuck immediately in the tissue near where they are laid, causing fibrosis and granuloma as the host tries to protect itself. Other eggs get washed to the liver and spleen where they may cause similar damage.

The medicines available to kill the schistosomes in people have so many dangerous side effects that they must be administered under medical supervision. They are costly. They do not protect a person in an endemic area against reinfection. Even if enough medical personnel were available to treat all the infected population in a single month, the snail (and sometimes nonhuman mammalian) reservoirs of infection would persist. The control or eradication of schistosomiasis is a truly ecological, as opposed to a purely medical or technological, problem.

PROPORTION EVER INFECTED AS A FUNCTION OF AGE

The mathematical models in this section and the next use cross-sectional data about a population presumed to be in steady state in order to make inferences about the dynamics of infection in a cohort.

Suppose a cohort is entirely susceptible to infection at some initial time, usually taken to be birth. Suppose that this cohort is exposed to a constant force of infection

per unit time. "This force is to be measured in effective contacts per unit time, no matter how complex may be the events leading up to these contacts" (42, p. 16). The force of infection a summarizes the contact between cercariae and people and the establishment of a detectable infection.

Let N be the number of individuals in the cohort. Let $x(t)$ be the fraction of the cohort that has never been infected, and $y(t)$ the fraction that has ever been infected, by time t. By definition $x(t) + y(t) = 1$. Assume $x(0) = 1$ and $y(0) = 0$. Then $Nx(t)$ is the number of individuals never infected at time t. These individuals are constantly exposed to a force a of infection. So the change per unit time in the number $Nx(t)$ of people never infected is $\mathrm{d}[Nx(t)]/\mathrm{d}t = -aNx(t)$, or, cancelling N, assumed constant, $\mathrm{d}x/\mathrm{d}t = -ax$, $x(0) = 1$. Similarly, for the number ever infected, $\mathrm{d}y/\mathrm{d}t = ax = a(1-y)$, $y(0) = 0$. The solution is

$$y(t) = 1 - e^{-at}. \qquad 1.$$

Death or emigration will have no effect on the fraction $y(t)$, so long as the loss rate (including death and emigration) is identical for both previously infected and never infected individuals (7).

If past conditions were constant, and all previous infections were detected, then (22) a cross-sectional survey should give a graph of the fraction of people ever infected as a function of age that looks like equation 1.

Figure 2 takes $t = 0$ as 5 years of age. Infections before that age are neglected. The data are the fractions of people in each age group judged ever to have been infected with schistosomes on the basis of a skin test. Particularly for the younger age groups, the fit of equation 1 to the data is reasonable. The discrepancy at the upper ages is explained as due to an insensitivity of the skin test to previous infection if the person has not recently been exposed to female cercariae or has no living female worms.

The numerical value of the parameter $a = 0.12$ used in Figure 2 was not obtained by fitting that curve to those data. The parameter was estimated by fitting another equation (number 5 below) to different data, from stool examinations, on the same population. This finding suggests that an incredibly simple mathematical model can usefully interpret the age distribution of previous infection and provide information about the dynamics of infection which would otherwise be unavailable.

PROPORTION CURRENTLY INFECTED

Female *S. mansoni* worms in human beings live an average of 3–4 years; other species of human schistosomes are comparable (21, p. 52; 29, p. 152). A negative exponential distribution of length of life for female worms is widely assumed. A person in whom all female worms have died no longer discharges eggs. (A person may also no longer discharge eggs because tissue traps the eggs or because living females are unmated. We ignore these complications.) Hence some individuals previously infected may pass from currently discharging eggs to no longer doing so.

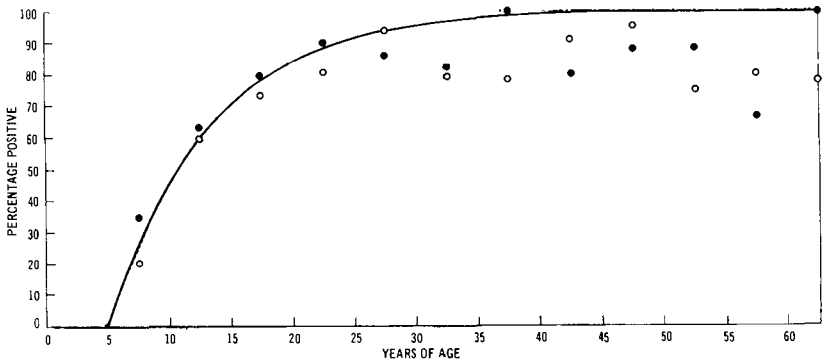

Figure 2 The proportions observed positive in response to *S. japonicum* antigen skin tests as a function of age in the coastal division, Palo, Philippines. Open circles, 1954; solid circles, 1962. Solid line, prediction from equation 1. [Adapted from (22), p. 172. Courtesy of Nelson G. Hairston and the World Health Organization.]

Irreversible Loss of Infection

Let us assume that a previously infected person who is no longer discharging eggs has no risk of reinfection. Let $y(t)$ (not the same as in the previous section) be the proportion of a cohort which is currently giving evidence of infection by excreting eggs. Let $z(t)$ be the proportion that has been previously infected, but is no longer passing eggs and has no risk of reinfection. As before, let $x(t)$ be the proportion which has never been infected. Assuming no death or emigration, $x(t) + y(t) + z(t) = 1$.

If the cohort is subject to a constant force of infection a, and those individuals currently giving evidence of infection are now further subject to a constant risk of loss of infection b, here assumed to be independent of the number of worms or worm pairs in the host, then under constant conditions the proportions x, y, and z are described (42) by:

$$dx/dt = -ax, \qquad x(0) = 1, \tag{2.}$$

$$dy/dt = +ax - by, \qquad y(0) = 0, \tag{3.}$$

$$dz/dt = +by, \qquad z(0) = 0. \tag{4.}$$

All individuals are uninfected initially. The sum of the derivatives is zero, as it must be since the cohort does not change size. Then:

$$y(t) = a(e^{-bt} - e^{-at})/(a-b), \quad \text{if } a \neq b; \tag{5.}$$

$$y(t) = ate^{-at}, \quad \text{if } a = b.$$

If death and emigration occur at equal rates in all three fractions of the cohort, the same equations hold.

Figure 3 plots $y(t)$ and the observed proportions with *S. japonicum* eggs in their feces by age in the same Philippine population pictured in Figure 2. Hairston (22) fits equation 5 by the method of moments (42). The annual rate $b = 0.02$ of becoming negative is not the annual death rate of individual female worms because (assuming the eggs are not blocked in the person's tissues) all the females in the person have to die, without replacement, for the person to stop passing eggs. Lewis (33) refits the same data by maximum likelihood, with similar results.

The model's assumption that an individual's probability per unit time of losing infection is independent of the individual's age, immune status, duration of infection, and worm burden means that the effects of varying other ecological parameters cannot be calculated. A micro-theory which interprets the model's parameters would be useful.

Snails too pass through the stages of being never infected, being infected and shedding (cercariae, instead of eggs), and (possibly) being no longer infected (53, 55).

Reversible Loss of Infection

Reinfection of previously but no longer infected individuals is observed. At the opposite extreme from the assumption just made that a loss of infection is irreversible is the assumption that a person no longer infected is exposed to a risk of infection identical to that of a person never previously infected.

If, as in the previous model, it is assumed that the instantaneous rates of infection a and of loss of infection b are constant, then the model is identical to one widely used for malaria and other diseases (17). All else being constant, this model predicts

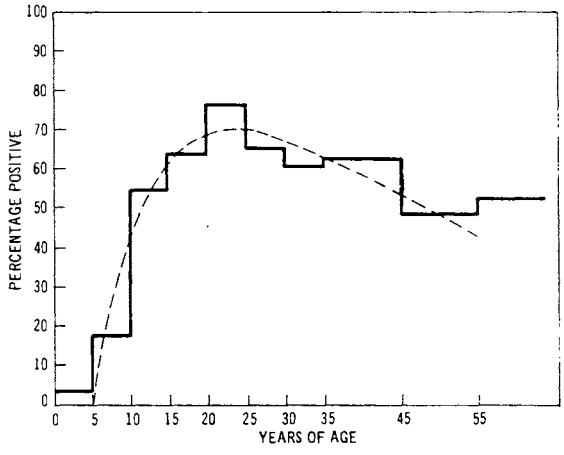

Figure 3 Observed age-specific prevalence rates (solid line) and theoretical age-specific prevalence rates (dashed line) from equation 5 of human infection with *S. japonicum* in the coastal division, Palo, Philippines, neglecting transmission before 5 years of age. [From (22), p. 171. Courtesy of Nelson G. Hairston and the World Health Organization.]

a prevalence rate which increases monotonically to an asymptote, contrary to observation (Figure 3). The assumption of reversible loss of infection is retained in a modified form of this model used for economic evaluation (50, 51).

The assumption of completely reversible loss of infection has appeared in models which view the number of worms in each human host as an immigration-death process (25, 34, 43–47). A risk of infection which is constant in time, or independent of age in a cohort, implies a monotonically increasing prevalence rate of humans who carry at least one mated pair of worms (26). Assuming that the risk of infection decays negative exponentially with increasing time (or age) to some positive lower asymptote predicts an age prevalence curve that fits observations of *S. mansoni* and *S. haematobium* reasonably and gives estimates of the life expectancy of the worms compatible with other findings.

Neither completely irreversible nor completely reversible loss of infections seems likely. Intermediate possibilities are discussed in the section below on immunity.

Differential Mortality Due to Infection

For people, the increment, if it exists, in the probability of death at any age due to infecting schistosomes has never been measured credibly (8, 9). Snails shedding cercariae of *S. mansoni* show an increase in death rate compared with uninfected snails.

If μ is the mortality or emigration rate of individuals not currently shedding eggs (in the case of humans) or cercariae (snails), and $\mu + \epsilon$ is the increased mortality or emigration rate of individuals currently shedding, then suppose, assuming irreversible loss of infection,

$$(1/N)\mathrm{d}(Nx)/\mathrm{d}t = -ax - \mu x, \qquad x(0) = 1, \tag{6.}$$

$$(1/N)\mathrm{d}(Ny)/\mathrm{d}t = +ax - by - (\mu + \epsilon)y, \qquad y(0) = 0, \tag{7.}$$

$$(1/N)\mathrm{d}(Nz)/\mathrm{d}t = by - \mu z. \qquad z(0) = 0. \tag{8.}$$

When $\epsilon = 0$, putting $N(t) = N(0)e^{-\mu t}$ leads back to equation 5.

If $y(t)$ obtained from equations 6–8 is a better approximation to reality than equation 5, but a curve of the form of equation 5 is fitted to data in ignorance of ϵ, then the resulting estimates of the parameters a and b may be biased (8). For humans, the differences are small among the age prevalence curves predicted by assuming that all the bias is absorbed either by a or by b, although the possible bias in the parameter estimates is not. For snails, even the possible bias in the parameter estimates is small (53).

This example illustrates a sensitivity analysis which can profitably accompany the study of ecological models. The model with differential mortality is more realistic than the model without it because differential mortality does occur. The more complicated model is more complicated to study mathematically. It does not cause major alterations in how the age prevalence data are understood. Hence, for rough purposes, one can be more assured of the adequacy of equations 2–4; for finer purposes, one has a more refined tool, equations 6–8.

Latency

The lag or latency of several weeks between the infection of a person with cercariae and the appearance of eggs in feces or excreta is short compared to the 1–5 year age groups used in collecting human prevalence data, and very short compared to the human life span. Hence the assumption of an instantaneous transition from uninfected status to detectably infected status may serve adequately for humans.

With snails, however, the lag of 4–5 weeks exceeds the one week age grouping ordinarily used for age prevalence curves and is a substantial fraction of the snail life span. Nasell (45) distinguishes "exposed" snails infected by miracidia from those shedding cercariae, and derives the age prevalence curve of infective snails. Susceptible, exposed, infective (or shedding), and recovered (or no longer shedding) snails each have a characteristic death rate:

$$dx/dt = -ax - \mu_1 x, \qquad x(0) = 1, \quad \text{(susceptible);} \tag{9.}$$

$$du/dt = +ax - Au - \mu_2 u, \qquad u(0) = 0, \quad \text{(exposed but latent);} \tag{10.}$$

$$dy/dt = +Au - by - \mu_3 y, \qquad y(0) = 0, \quad \text{(infective, shedding);} \tag{11.}$$

$$dz/dt = +by - \mu_4 z, \qquad z(0) = 0, \quad \text{(no longer shedding).} \tag{12.}$$

The fraction of the cohort infected, $y/(x + u + y + z)$, need not vanish with increasing time if the mortality μ_4 of recovered individuals is large enough.

This model implies that the distribution of the interval from successful infection of a snail by a miracidium to the first shedding of cercariae should be negative exponentially distributed, with the parameter A which appears in equations 10 and 11. The mode of such a distribution is at intervals of length zero, contrary to observation.

In a model which incorporates real latent periods between infection and infectivity, Lee & Lewis (32) estimate the latent period in humans to be 2 months. In snails, the latent period is taken to vary from 5 months in the cool season to 1 month in the warm. The implied age prevalence distribution in humans or snails is not shown.

Immunity

In trying to explain why observed human age prevalence distributions of schistosomiasis initially peak and then decline with increasing age, some medical authorities (3) emphasize the importance of human immunity. Others (58) emphasize declining human contact, for cultural and behavioral reasons, with cercariae-laden water. The fitting of models to age prevalence distributions cannot decide the relative importance of these two explanations. An immigration rate of worms to humans which declines with age may result either from immunity to new infections or from declining water contact (26).

The same qualitative effect is obtained (33) by assuming a constant immigration rate and a temporary immunity following loss of infection in a modified two-stage catalytic model. The modified model yields a substantial and statistically significant improvement in fit to Hairston's (22) data on *S. haematobium* and *S. mansoni,* but

describes the *S. japonicum* data no better than equations 2–4. Let $x(t)$ and $y(t)$ be interpreted as in equations 2–4. Let $z(t)$ be the proportion of a cohort that was previously infected, which now no longer shows patent infection, and which is now temporarily immune. Assume that immune individuals are subject to a constant risk c of loss of immunity, after which they are as susceptible to reinfection as individuals never previously infected. Thus:

$$dx/dt = +cz - ax, \qquad x(0) = 1, \tag{13.}$$

$$dy/dt = +ax - by, \qquad y(0) = 0, \tag{14.}$$

$$dz/dt = +by - cz, \qquad z(0) = 0. \tag{15.}$$

For certain parameter values the proportion $y(t)$ of infective individuals initially increases with age, peaks, and then decays exponentially to a positive limit $ac/(ab + ac + bc)$. For other parameter values, $y(t)$ performs damped oscillations in approaching this limit. When $c = 0$, immunity is permanent and this model reverts to equations 2–4.

Lewis (33) extends the model of equations 13–15 by recognizing that an individual never previously infected can shed eggs only if it has been infected by at least one male and at least one female worm. Male and female cercariae are assumed equally likely to enter a host never previously infected, in a Poisson stream with constant parameter. Assuming that worms of the opposite sex survive from a previous infection, previously infected individuals who have lost their immunity require infection only by one more cercaria in order to reestablish infectivity. In this model, permanent immunity can again be represented by taking $c = 0$.

This model describes Hairston's (22) *S. japonicum* data better than equations 13–15, primarily owing to the representation of sexual pairing of worms.

Linhart's (37) predicted age prevalence curves have not been tested against observations, except where they coincide with the two-stage catalytic model.

At each time t in Linhart's three models, every individual is either manifest (showing proof of current worms according to some test) or not. An individual not manifest at t but manifest before t is called cured at t. Every individual is also either immune or not immune at each time t. Immunity is permanent, once achieved. An infection is defined as the attempted entry of cercariae into the individual. An infection is ineffective if the individual is immune at the time, effective otherwise.

Infections arrive as a Poisson stream with parameter α. Let $t_1, t_2, \ldots$ denote the times at which the first, second, ... infections occur.

The first model assumes that an individual becomes manifest at t_1. The assumption would be reasonable if the definition of "manifest" were based on a serological or other assay of the metabolic products of a single schistosomule (30).

The model assumes that the individual becomes immune and cured at $t_1 + c + b$, where c is a nonnegative constant delay and b is a random variable with negative exponential distribution and parameter β. The expected fraction manifest at time t in a cohort not subject to differential mortality or emigration, is

$$y(t) = 1 - e^{-\alpha t}, \qquad t \leqslant c,$$

$$= e^{-\alpha t}(e^{\alpha c}-1) + \alpha[e^{-\beta(t-c)} - e^{-\alpha(t-c)}]/(\alpha-\beta), \qquad \alpha \neq \beta,\ c \leqslant t. \tag{16.}$$

If $c = 0$, this equation becomes identical to equation 5 when the stochastic rates α and β are replaced by their corresponding deterministic equivalents a and b.

The second model assumes that an individual becomes manifest at t_1 and immune to any further infections at $t_1 + c$, where c is a positive constant. Between t_1 and $t_1 + c$, further effective infections may occur. If the last of these occurs at t_k, then the individual becomes cured at $t_k + d$, where $d \leqslant c$ is a constant. Under these assumptions,

$$\begin{aligned} y(t) &= 1 - e^{-\alpha t}, && 0 \leqslant t \leqslant d, \\ &= 1 - e^{-\alpha t} - (1/2)e^{-\alpha c}[e^{\alpha(t-d)} - e^{-\alpha(t-d)}], && d \leqslant t \leqslant c+d, \\ &= e^{-\alpha t}\{[e^{\alpha(c+d)} + e^{-\alpha(c-d)}]/2 - 1\}, && c+d \leqslant t. \end{aligned} \tag{17.}$$

The third model (37) assumes (again) that an individual becomes manifest at t_1. The individual becomes immune and cured when his "infection time" mounts up to a positive constant threshold w. If an individual has received k effective infections by t, then his infection time $I(t)$ at t is $I(t) = \sum_{j=1}^{k} (t - t_j)$, where t_j is the time of the jth effective infection. Every infection is assumed to be effective as long as $I(t) \leqslant w$. The probability that an individual is manifest is just the probability that $0 < I(t) \leqslant w$. Hence, for given t, if s is the integer satisfying $st \leqslant w < (s+1)t$,

$$\begin{aligned} y(t) = e^{-\alpha t}\{&\textstyle\sum_{k=0}^{s} [\alpha t]^k/k! - 1 \\ &+[\textstyle\sum_{k=s+1}^{\infty} \alpha^k/k!]\ \sum_{j=0}^{s} [-1]^j[w-jt]^k/[j!(k-j)!]\}. \end{aligned} \tag{18.}$$

Biological Aspects

An important task in the modeling of schistosomiasis is to translate the burgeoning biological information about the immunology of schistosomiasis into mathematically explicit, empirically testable, and epidemiologically useful form.

It would seem useful to develop, and to test against data, a model incorporating: (*a*) a risk of exposure to cercariae which is variable with age, season, and infection status; (*b*) sexual pairing of worms (see below); (*c*) true latency between infection and the first shedding of eggs; (*d*) a risk of loss of apparent infection dependent on worm load, age of worms (since older worms may lay fewer eggs), and age of host (since long-term pathology may interfere with the escape of eggs); (*e*) concomitant immunity, in which the host's response to established infections inhibits superinfection; (*f*) subsequent immunity, in which the host's response to previous infections inhibits reinfection; (*g*) a decay of immunity. Quantitative tests against varied age prevalence data and against direct observations of the component processes assumed

in the model might lead more rapidly than the present piecemeal approach to a focus on the features important for a control of prevalence.

SNAIL POPULATION DYNAMICS

The models considered so far are implicitly conditional on the invariance of the half of the schistosome life cycle which is not being modeled. For example, the studies of human prevalence assume the supply of cercariae from snails is steady in time.

Food and Crowding

Biomphalaria glabrata is the snail principally responsible for the transmission of *S. mansoni* in the New World. Jobin & Michelson (28) raised laboratory populations of these snails with varying amounts F of food (measured in grams of watercress), numbers N of snails (each 15 mm in diameter), and volumes V of water (4.5 and 7.6 liters), at 25°C. For each such population they measured the fecundity (E) by the numbers of eggs laid per snail per day (Figure 4):

$$E = kF/NV. \tag{19.}$$

It is plausible that, over a certain range at least, fecundity should increase with food and decrease with the number of snails competing for that food. What is counterintuitive about equation 19 is that a larger volume of water *decreases* fecundity. The reason is that in larger volumes of water the snails have a harder time finding the food.

In very large volumes of water, such as lakes, which are not crowded with snails, the addition of one more snail has no effect on the fecundity of the other snails present. So Jobin & Michelson (28) assume that the inverse dependence on N in

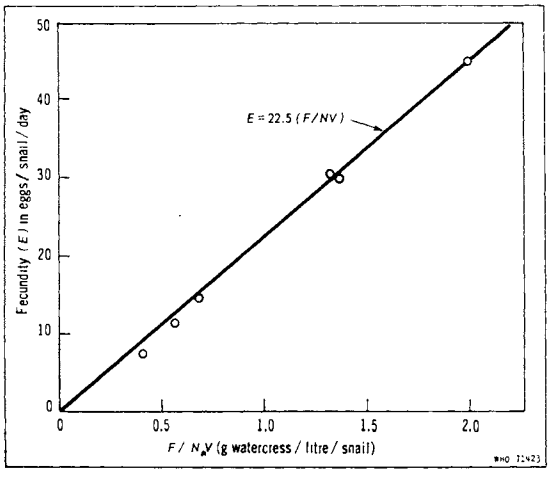

Figure 4 Fecundity of *Biomphalaria glabrata* snails as a function of food F, number N of snails, and water volume V. [From (28), p. 659. Courtesy of E. H. Michelson and the World Health Organization.]

equation 19 disappears whenever the volume of water per snail exceeds some threshold.

Since, moreover, equation 19 predicts that snails in a vanishingly small volume of water have an infinite fecundity, equation 19 should be regarded as a linear approximation to a nonlinear function over the range of variables used in one set of experiments.

In a simulation, the proportionality constant k becomes a function of the species and age of the snails, the nutritional value of food, and water temperature. Mortality is assumed to depend on demographic and ecological factors. The parameters are estimated from observations by another investigator of *Bulinus globosus,* a Rhodesian snail carrying *S. haematobium.* The predicted snail populations agree roughly with censuses. Sensitivity analysis with respect to both parameter values and the form of entire components of the model would be desirable.

Infection and Age Structure

Coutinho & Coutinho [(12); see (13) for errata] explain two generalizations from previous empirical work. The first generalization is that $D = A/(B + p)$, where D is an index of the size of *B. glabrata* snails in a lake and p is the prevalence rate among those snails of infection with *S. mansoni.* A and B are constants.

The explanation offered is that higher prevalence is associated with a higher force of mortality due to infection. A higher force of mortality results in a younger age structure in the population, or a smaller probability that any egg will survive to any given age. Since younger snails are smaller than older snails, a higher prevalence is associated with a smaller snail population. By suitable quantitative assumptions, $D = A/(B + p)$ follows.

The prevalence rates in the 12 lakes reported (12) vary from 0.6% to 8.3%. It would be desirable to represent the life table in these lakes as a mixture of two negative exponential life tables, one with low mortality for the uninfected majority and one with high mortality for the infected minority, rather than assuming a single negative exponential life table as at present.

The explanation offered (12) overlooks the direct inhibitory effect (54) of being infected on snail growth. The inverse relation between snail size and prevalence of infection in different populations very probably results from the effect of infection on both snail growth and mortality.

The second generalization is that "when the infection rate [prevalence rate p] was small, the snails, even though they attained a large size, were less abundant, whereas in sites of greater infection rate which caused smaller shell sizes the abundance per unit area was considerably higher."

The explanation offered assumes that the quantity of food consumed by the snails per unit time and per unit area is constant, and therefore that the supportable biomass of snails is constant from one lake to another. When the mortality due to infection is small, a higher proportion of snails survives to older ages. Being bigger at older ages, those snails consume more food, leaving less for the many small snails. Hence the total number, or abundance, of snails is less than when mortality due to infection is large.

Direct evidence for the constancy of the food supply or the biomass density is not offered. If F is constant, and if the variation in V in equation 19 from one lake to another is negligible, then according to equation 19, the fecundity E is inversely proportional to the abundance N of individuals without regard to their size. Thus lower abundance N should be associated with a higher fecundity E which, all else being equal, should (by standard demographic arguments) be associated with a younger age structure, that is, typically smaller snails. Evidently not all else is equal, because the size index is larger where the snails are less abundant (12). It would be desirable in future work to reconcile the generalization, equation 19, from laboratory work, with the second generalization, based on field work. Measurement of N in terms of biomass, rather than numbers, might suffice.

Coutinho & Coutinho (13) adduce a similar explanation for observations that the maximum diameter of snail shells in a uniform, swiftly flowing channel increases from the input to the outlet of the channel. Along the same axis the number of snails per unit of channel length decreases progressively. Subsequently, Coutinho & Coutinho (14) study the age structure of a snail population resulting from a time-varying, age-independent cause of mortality.

Other Treatments

Nasell & Hirsch (45–47) take the population of snails to be constant, either always or asymptotically. Lewis (34) models the snail population as a stochastic immigration–birth–death process. The linear birth and death rates for susceptible snails are not assumed to be the same as those for infected snails. These models are components of life cycle models (below).

SEX AMONG THE SCHISTOSOMES

Only mated adult worms produce the eggs which are believed to be the primary cause of schistosomal pathology when they do not escape from the human host (36), and which sustain the transmission cycle when they do escape. Mathematical models of mating quantify possibilities within the range of present ignorance.

Monogamy

Assuming monogamous pairing, if a person is infected with an even number n of worms, each of which is male or female with probability 1/2, then (38) the probability that a given larva is matched by one of opposite sex, or the expected proportion of worms that are matched, is $1 - n!/\{[(n/2)!]^2 2^n\} \approx 1 - 0.7979n^{-1/2}$. When n is odd, the probability that a larva is matched is the same as that for the preceding even number. This probability of matching is not necessarily identical to the probability of mating heterosexual pairs, because the members of each pair have to find each other in the dark, but Hairston (personal communication) knows of no record of mature worms of opposite sexes remaining unmated.

Suppose (16, 20, 21, 37, 38) that the number of larvae per person is Poisson-distributed with a mean, say, of m larvae. Then the proportion of larvae matched

by one of the opposite sex, averaged over all people, is $\Psi(m) = 1 - e^{-m}[I_0(m) + I_1(m)]$, where I_n is the modified Bessel function of the first kind of order n (Figure 5). Nasell (43) corrects Macdonald's formula 7 (38, p. 503) and obtains the simple expression for $\Psi(m)$ just given. It is assumed that pairs are strictly monogamous and that a worm that dies is immediately replaced by another worm of the same sex.

The expected proportion of people with at least one potential heterosexual pair of worms (the prevalence, as usually assayed) is $(1 - e^{-m/2})^2$, again assuming monogamy and a Poisson distribution of larvae. This expression, due to Hairston (unpublished) and, independently, Nasell (43), simplifies a result of Macdonald's [(38), p. 504, equation 10].

Suppose (47) that the male and female worms are subject to identical independent processes of immigration and death, where the risk of death is constant for all age and sex classes of worms and hosts. At equilibrium in a life cycle model, the immigration rate of larvae becomes constant, over time and over people. If ρ is the ratio of the equilibrium immigration rate of worms of either sex per host to the constant rate of death per worm, then $m = 2\rho$ and the average number of mated pairs of worms per person in the population is $(m/2)\Psi(m) \sim m^2/4$ as $m \to 0$, and $\sim m/2$ as $m \to \infty$.

Tallis & Leyton (56) study this immigration–linear-death model as well as contagious arrivals and age dependent deaths.

Assuming equilibrium in the input of cercariae, suppose that male and female larvae enter a person according to independent identical Poisson processes with

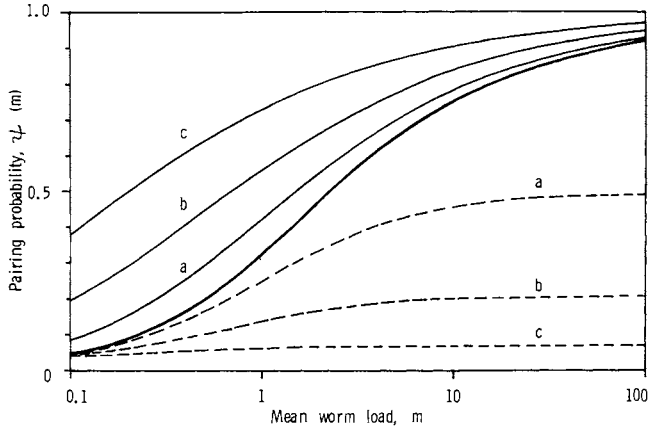

Figure 5 The proportion $\Psi(m)$ of adult worms that can be paired monogamously with an adult worm of opposite sex as a function of the mean worm load m per host, under various assumptions about the distribution of worms. Heavy solid line: Poisson distribution; light solid lines: negative binomial distribution, with both sexes together; light broken lines: negative binomial distribution, with both sexes separate. The coefficient of variation increases from *a* to *b* to *c*. (Courtesy of Robert M. May.)

constant parameter, and that when a mated worm dies, its former partner does not remate (16). Under the same definition of ρ, the expected number of paired worms per host then approximates ρ^2 as $\rho \to 0$, but $\rho/2$ as $\rho \to \infty$. For large ρ or m the assumption that a mated worm does not remate after the death of its partner leads to half as many expected worm pairs as Macdonald's assumption.

Diversity

Apparently independently of Macdonald (38), Leyton (35) studies several possible modes of reproduction in helminthic infections. He relates the distribution of the number of worms laying eggs to the bivariate distribution of the numbers of sexually mature male and female worms, allowing the worm population's size distribution to be general.

Assuming parthenogenesis, any female can lay eggs. The distribution of egg-layers is the marginal distribution of female worms.

Assuming hermaphroditism, every worm can fertilize itself, though cross fertilization can occur. The distribution of egg-layers is the distribution of the total number of worms.

Assuming monogamous heterosexual mating, and the remating of widowed worms [the case considered by (47)], Leyton (35, p. 418) finds the probability distribution of the number of egg-layers. He also (35, p. 419) writes out explicitly the distribution of egg-layers assuming a (bivariate) negative binomial distribution of worms per host.

Leyton (35) also obtains the general distribution of egg-layers under the assumption that each male can mate up to k females (and that only mated females lay eggs). If a single male renders every female present an egg-layer, the distribution of egg-layers is a simple function of the numbers of males and females.

Overdispersion

Almost certainly in real human populations the variance in the number of infecting worms significantly exceeds the mean (2, 15), even within particular age and sex groups. As analytically tractable approximations to the distribution of adult worms, there are two overdispersed extreme alternatives to a Poisson distribution of worms (4, 41).

First, when worms of both sexes are distributed "together," assume that the total number n of worms in a human host is negative-binomially distributed and that each worm is equally likely to be male or female; that is, conditional on n, the number of male or female worms is binomially distributed with parameters n and 0.5. The negative binomial distribution may be parameterized in terms of its mean m (as for the Poisson distribution above) and an index k which is inversely related to overdispersion. When k is infinite, the negative binomial becomes the Poisson distribution; when $k = 1$, it becomes the geometric; and as k vanishes, the distribution becomes increasingly overdispersed.

The second alternative to a Poisson distribution assumes worms of both sexes are distributed "separately": the number of males in a host is negative binomial with mean $m/2$, and similarly for the number of females, and males and females are

independent. The average number m of worms per host is therefore assumed to be the same, whether the males and females are distributed together or separately.

Worms of both sexes are likely to be distributed together where people are exposed to infection from snails with a high prevalence of infection (4). If the prevalence of snail infection is low, however, a person is more likely to be exposed to cercariae of only one sex, and the model of separate infections may be more appropriate.

The expected proportions of worms that are mated under the two assumptions differ from the Poisson expectations (Figure 5) in opposite directions. When both sexes are distributed together, the proportion mated always exceeds the proportion under the Poisson model. The difference is least when the mean worm load is high, which is when the assumption that the sexes are distributed together is most plausible. When the sexes are distributed separately, the proportion mated is always less than the proportion under the Poisson model. The difference is smallest at low worm loads where the model of independent distribution of the sexes is most plausible.

Biological Aspects

These studies point to several needs for additional biological information.

Which of the several models of mating considered by Leyton (35) and others actually holds? Hairston reports (unpublished) that *S. japonicum* is certainly not monogamous. In animals experimentally infected with an excess of females, all the females become mated and carry the full complement of eggs in utero; the same appears to hold for *S. mansoni.*

The public health impact of the difference between monogamy of worm pairs (38, 47) and faithfulness after death (16) depends on the causes of schistosomal pathology. Pathology due to metabolic products or simply the presence of worms may be presumed proportional to the total number of worms [as in (37)]. If the pathology were primarily due to eggs laid, and if only currently mated females could lay eggs, then faithfulness after death would be important. If the pathology were primarily due to eggs laid, but any female once mated could continue to lay eggs, then the relevant variable, namely number of females ever mated, has not been investigated.

Are the assumptions of Nasell & Hirsch (47) regarding the equality of male and female worm death rates close to true? Lewis (34) takes the death rate of worm pairs to be that of the female worms. Some evidence suggests this assumption may be preferable.

Since a female worm must leave the male's gynecophoric canal to lay eggs in the person's small blood vessels, she is more exposed than the male to damage by the host's reactions and suffers a higher death rate (20, p. 51). Human autopsies consistently show an excess of male worms at all levels of infection [(5, p. 45); his Table 3] and in all human age groups [(5, p. 52); his Table 12]. There is no tendency for the fraction of worms that are female to change with host age, however.

The death rate of worms may also be density dependent, rising due to crowding in people with a large number of worms.

How overdispersed are adult schistosomes in human populations? Under what circumstances are the two sexes distributed jointly together or separately? If the

sexes are independently distributed at low average worm prevalence and together at high, then the sensitivity analysis of models of Bradley & May (4) offers assurance that deviations from a Poisson distribution are no cause for great concern. If the sexes are distributed otherwise, then it is important to know how before implementing recommendations which presuppose a Poisson distribution of parasites.

LIFE CYCLE MODELS

Some models attempt to comprehend the entire schistosome life cycle (20, 21, 25, 32, 34, 38, 43–47).

A Life Table Model

In Palo in the Philippines (20, 21), the proportion of people infected with *S. japonicum* at each age changed very little from 1945 to 1959. Hence it is plausible that the per capita risk of infection also changed very little over that period. Barring large changes in the human population, the total worm population must have been stationary (constant in total numbers and age structure). The demographic model of a stationary population, a life table, therefore may describe the population of *S. japonicum* there.

In this model, the net rate of reproduction *NRR* of the worm may be written as the product of four factors reflecting four major stages in the worm's life cycle. The worm's *NRR* is equal to the larval *NRR* in the snail, times the cercariae's probability of infecting a mammal, times the adult worm's *NRR* in the mammal, times the egg's probability of infecting a snail. Each factor decomposes further. For example, the probability of an egg's infecting a snail is the product of the probability that an egg is able to hatch, times the probability that the egg is deposited near snails, times the probability of penetrating a snail, times the probability of establishing an infection in the snail after penetration (21).

The estimate of *S. japonicum's NRR* is 0.6. Based on less reliable data from Egypt, the estimate for *S. mansoni* is 1.9 and for *S. haematobium* is 2.8. If the model and observations were correct, these estimates should be 1. That the estimates do not differ from 1 by orders of magnitude indicates the coherence of the observations and the approximate correctness of the model, under the given conditions.

Still, some qualifications deserve note. First, the deviation of the worm's *NRR* from 1 which was necessary to maintain constant prevalence rates in the growing human population was probably much less than the uncertainty of the data. Second, the independence of the elementary events which make up the life cycle is so unlikely that Hairston (20, 21) avoids the assumption in practice by estimating from his data, not the elementary probabilities that appear as factors in some of his formulas, but clusters of these factors representing compound events. Third, since "the parasite population is able to come into equilibrium at different rates of transmission" in different ecological settings, "net reproduction in one or both of the hosts must be curtailed with increasing transmission and enhanced with decreasing transmission." Hence "there is a range of transmission rates over which compensatory mechanisms

operate to keep the parasite population in equilibrium" (21, pp. 46–47). This means that if an intervention program reduces one of the four factors that determine the worm's *NRR,* over at least some range, the product of the other factors will increase to keep the worm's *NRR* near 1. Hairston (20, p. 52) estimates quantitatively the inhibiting effect of increasing the number of female worms of *S. japonicum* present in a person of specified age on the average daily number of eggs in feces per female worm. Similarly, in human autopsies, not based on a randomly sampled population, among so-called "asymptomatic" cases of *S. mansoni,* the mean number of eggs per gram of feces per worm pair may decline with increasing numbers of worm pairs [(5, p. 45); his Table 3, where worm pairs are defined as the lesser of the number of male and female worms recovered]. Animal experiments show that increasing parasite loads decrease reproductive output per parasite (31).

As a result of such compensatory mechanisms (3), one cannot use Hairston's calculated values of the worm's *NRR* factors in a simpleminded way when evaluating a control program that affects the values of some of those factors.

Hairston (21, p. 47) guesses that in schistosomiasis, "the most important cause of the failure of compensatory mechanisms at low transmission rates is the increasing probability that single parasites which succeed in entering the definitive host [man] will remain unmated."

Without belaboring the calculations, he explicitly [(20), his Figures 2, 3, 5] uses the chances of being mated, as well as the effects of crowding of worms within the human host, in estimating the mean number of hatchable female eggs per female worm per day as a function of mean worm load and in estimating the *NRR* of female worms in humans as a function of mean worm acquisition rate.

These calculations were overlooked by Macdonald (38) who cited Hairston's (20) paper. Macdonald is generally, but inaccurately, credited with introducing the role of pair formation in schistosome models.

Dynamic Models

Dynamic models aim to describe what will happen when the life cycle is perturbed. To represent the compensatory mechanisms which regulate population numbers they must be nonlinear. One such model (38) emphasizes the nonlinearity introduced by supposed monogamous mating in the sexual stage of the worms, and borrows other nonlinear bits from existing models of malaria. Numerical analysis of this model suggests the existence of a threshold in m, the mean worm load in people. Once m is below this threshold, transmission of infection disappears in a few years; once above it, infection remains endemic indefinitely.

Macdonald (38, p. 500) claims that a very high level of environmental sanitation, meaning a great reduction in the number of eggs reaching water, has a negligible effect on the mean worm load compared to the combined effects of treating infected people and keeping them out of infected water. This conclusion results from Macdonald's implicit assumption, not generally true, that the water in which snails live is saturated with miracidia and that nearly all snails are infected [(23) and N. G. Hairston, unpublished].

Hybrid Dynamic Models

Nasell & Hirsch (47) assume a fixed number N_1 of humans and fixed number N_2 of snails. The state of the model is specified by the number $M_k(t)$ of male and the number $F_k(t)$ of female worms at time t in each person, $k = 1, 2, \ldots N_1$, and by the number $S(t)$ of infected snails.

Individual people may differ in the number of worms they carry initially, but are otherwise subject to identical Markovian laws. Each worm in a person has a fixed probability intensity μ_1 per unit time of dying, identical to and independent of all other worms. (This μ_1 is not the same as in equation 9 above.) New worms enter a person at a rate $\nu_1 E[S(t)]$, which is proportional to the *expected* number of infected snails at that time. Nasell's use here of the expected, rather than actual, number of infected snails makes this model a hybrid of stochastic and deterministic elements.

Every infected snail has an identical and constant death rate μ_2; every snail that dies is replaced instantaneously by an uninfected snail. Each uninfected snail risks infection at a rate which is proportional to the *expected* number of mated worm pairs in all the human hosts put together, with proportionality constant ν_2.

The model explicitly (47, p. 401) ignores the possible influence of human age and sex on human infection rates; the effect of worm and snail age and population density on worm and snail death rates, respectively; the effect of age on egg-laying by female worms and on cercarial shedding by snails; as well as the development of resistance to infection and of latent periods.

In a closed community, with no infection from without, let $W(t)$ be the expected number of worms invading an individual person since time 0 and still alive at t, let $X(t)$ be the expected number of monogamously mated worm pairs in all people added together, and let $Y(t) = E[S(t)]$ be the expected number of infected snails at time t. Then

$$\begin{aligned} dW/dt &= -\mu_1 W + \nu_1 Y, \\ dY/dt &= \nu_2 X(N_2 - Y) - \mu_2 Y. \end{aligned} \qquad 20.$$

Since $X(t)$ is a complicated but explicit function of $W(t)$ and of t, $X(t)$ may be eliminated to give a pair of differential equations in W and Y. To study the asymptotic behavior of the solution(s) of these equations, introduce two "transmission factors" $T_1 = \nu_1 N_2/\mu_1$ and $T_2 = \nu_2 N_1/\mu_2$. T_1 measures the maximum ability of the snail population to deliver live schistosomes to a person, because it is the product of the ability ν_1/μ_1 of the one infected snail to deliver schistosomes times the maximum number N_2 of infected snails. T_2 measures the ability of the human population to deliver live miracidia to an uninfected snail.

Asymptotically equations 20 have one, two, or three critical points (points where the derivatives are zero), depending on a relation between the transmission factors. A human population will ultimately move to a level of infection corresponding to

one of these critical points. If the human population initially has a nonzero worm load, and if the transmission factors lie above a certain threshold function, then the critical point reached asymptotically depends on that initial level of infection.

Control of infection is a practical problem only when, in addition to the stable critical point corresponding to the elimination of infection, there are two critical points with positive levels of infection in people and snails. One of these points is stable, the other not. Nasell (46) considers the possibility of controlling the initial conditions of infection in the human and snail populations. Nasell & Hirsch (47, pp. 444 ff.) study changes in the transmission factors.

If costs to diminish a transmission factor are proportional only to the percentage reduction obtained, but are otherwise the same for both transmission factors, then a strategy of reducing T_1 is more efficient than a strategy of reducing T_2. This conclusion has been interpreted as supporting Macdonald's (38) claim that control of human feces by sanitation is a worse strategy than snail control. The applicability of the conclusion depends on the parameter values and costs which must be evaluated in each application (see below).

Nasell observes (unpublished) that if Hairston's condition for stationarity is translated into the notation of his model it becomes $T_1 T_2 \Psi(m)\ (1 - Y_\infty/N_2) = 2m$. This equation specifies a relation which must hold between the mean worm load m in people and the expected prevalence rate of infection among snails Y_∞/N_2 at equilibrium in Nasell's model.

The introduction of latency in snails (45) does not alter the qualitative conclusions drawn from the model.

Nasell (44) extends the model (47) by assuming that a source of infection external to the community adds to the infection rate per uninfected snail a constant ϵ_2 and adds to the rates of infection of people by male and by female cercariae each a constant $\epsilon_1/2$. Let $\delta_1 = \epsilon_1/(\nu_1 N_2)$ be the increase in the proportion of infected snails that would be equivalent in the effect on people to the external source of cercariae. Let $\delta_2 = \epsilon_2/(\nu_2 N_1)$ be the increase in the mean number of paired female worms per person that would be equivalent in the effect on snails to the external source of miracidia or eggs. T_1 remains a more efficient control of mean worm load m than T_2, assuming equal costs for equal proportional reductions. Further, T_2 is a more efficient control than δ_2, which measures the external input of miracidia or eggs. The transmission factor T_1 is similarly a more efficient control than δ_1.

The asymptotic mean worm load m in humans as a function of the transmission capacity T_2 of eggs from people to snails is shown in Figure 6. Each curve corresponds to a different input δ_2 of eggs. All the curves correspond to the same transmission capacity T_1 of cercariae from snails to people and the same external input δ_1 of cercariae. For the largest value $\delta_{2,III}$ of external input of eggs (the uppermost curve), the only way to reduce m is to lower T_2 (all else held constant), and m varies smoothly as T_2 varies.

For external egg inputs such as $\delta_{2,I}$ and $\delta_{2,II}$ which are smaller than a certain threshold, the initial levels of infection in people and snails determine whether m will fall on the lower curve or on the upper curve. If m falls on an upper curve, then one dramatic possibility of control is to shift the initial conditions by coordi-

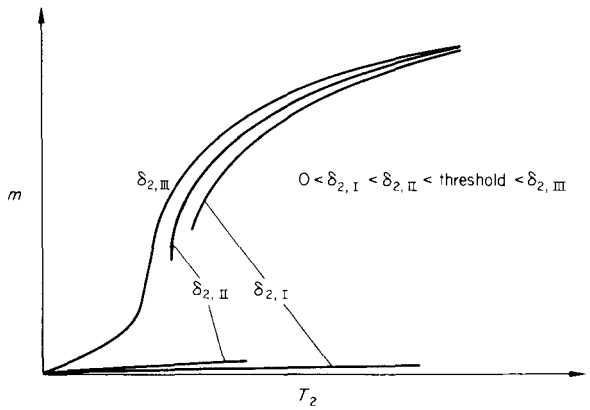

Figure 6 Asymptotic or equilibrium mean worm load m in humans as a function of the transmission capacity T_2 of eggs from people to snails, for various external egg inputs δ_2 and fixed cercarial transmission capacity and fixed external input of cercariae. [Adapted from (44). Courtesy of Ingemar Nasell.]

nated programs of human case finding and treatment so that m falls on the lower line. (When there is no external infection, the lower line is just the abscissa where $m = 0$.) This possibility leaves the community vulnerable to being transferred back to a higher value of m if an uncontrolled influx of infection effectively reverses the change in initial conditions. This possible mode of control arises discontinuously as a function of T_2 and of δ_2.

The curves shift if the parasites are overdispersed rather than Poisson-distributed (4). When worms of both sexes are distributed together, the discontinuities are decreased and the disease becomes harder to control. When worms of each sex are distributed separately, the discontinuities are emphasized, the possibilities of pushing initial conditions below a breakpoint or threshold are enhanced, and the disease becomes easier to control.

Now suppose (34) the human population varies as an immigration–death process, and immigrants are free from infection. Only worm pairs die (at the presumed death rate of females), instead of individuals independently. Instead of having a fixed number N_2 of snails, susceptible snails may immigrate; and both susceptible and infected snails may die and give birth at specific rates. The qualitative behavior of this more realistic hybrid model closely resembles that of the model of Nasell & Hirsch (47).

For one set of parameters, Lewis (34) compares the solution of his hybrid model with the average of ten numerically computed solutions of a fully stochastic model that is identical except for the hybrid simplifications. Since hybrid and stochastic solutions are very close, the hybrid approximations, introduced for mathematical convenience, are quantitatively useful in the range of parameters examined. See (34a) for threshold results.

A Delay Time Model

A deterministic model of Lee & Lewis (32), like that of (21), represents the human and snail populations implicitly through their effects on various stages of the parasite life cycle. All relationships are linear (e.g. eggs produced are directly proportional to the number of mated worm pairs) except for two: Only monogamously mated females are assumed fertile, following (38); and the proportion of miracidia that find snail hosts is assumed to decline nonlinearly with increasing numbers of miracidia per unit volume of water.

Time lags between the infection of snails and the emergence of cercariae, and between the infection of humans and the emergence of eggs, and the two nonlinearities, give the model a breakpoint, which varies seasonally because of the seasonality in the snail latent period. The relative timing of chemotherapy and the application of molluscicide is crucial in determining whether a combined attack using both can eventually eliminate infection.

Caveat Lector

Some models (19, 52; see 57) contain so many internal inconsistencies that they should be perused with extreme caution, if at all.

DECISION MAKING AND ECONOMICS

Sound ecological models of schistosomiasis are a necessary, but not a sufficient, condition for sound public decision making concerning the disease. Many of the models described so far compare strategies for control or eradication. Without reference to the social and economic costs and benefits of these strategies, these comparisons provide no guide for action. Because models which evaluate costs and benefits in relation to schistosomiasis go beyond the scope of ecology, we cite such efforts only briefly.

Using economic and demographic models and data from St. Lucia, a Caribbean island, Weisbrod et al (60) ask: Does infection cause disease? They find it impossible to evaluate the impact of *S. mansoni* on birth and death rates, the achievement of school children, and the labor productivity of adults without considering four intestinal nematodes of man which are also very widespread there.

Rosenfield (50, 51) evaluates the cost effectiveness of molluscicide use, environmental alterations, and chemotherapy, singly and in combination, using detailed data from a *S. haematobium* control project in Iran. Muench's (42) reversible catalytic model is modified to a discrete-time difference equation. The force of infection is estimated by regression as a Cobb-Douglas function of two variables: the meters of snail habitats accessible to the human population, and the number of infected persons. The combined strategy actually used yields a lower prevalence at the end of the project than would any of the three strategies used singly, within the same budgetary constraints.

Other quantitative approaches to evaluating the economic and demographic effects and costs of controlling schistosomiasis are available (1, 9, 10, 27, 39, 48, 49).

Though sound ecological understanding makes the task easier, a nation's ability to rid itself of schistosomiasis ultimately reflects social and political will (6).

ACKNOWLEDGMENTS

I thank Klaus Dietz, Nelson G. Hairston, Robert M. May, and Ingemar Nasell for criticisms, and the US National Science Foundation for partial support of some of the work described here.

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