Togetherness among Schistosomes: Its Effects on the Dynamics of the Infection

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ABSTRACT

This paper deals with the overall transmission dynamics of schistosomiasis, and other similar helminthic infections, in which the parasitic worms have a sexual stage in the primary (human) host. Most previous studies have assumed the worms to be independently randomly distributed among hosts; we explore the effects of various kinds of aggregation in the worm distribution, and their implications for medically interesting quantities such as prevalence of worms, prevalence of pairs, and mean egg output per host. The effects of worm aggregation upon the transmission dynamics are discussed, with particular regard to the "threshold" and "breakpoint" phenomena. It is shown that the analysis can be extended, simply but generally, to include the effects of a latent period before infected snails become infective. Most of the presentation is for a monogamous worm mating system, but the opposite extreme of promiscuous worms is also treated (in Appendix C). Although mainly concerned with these new results, the paper also attempts a limited amount of review and synthesis. This includes: relationships among earlier models; the threshold's dependence on the transmission parameters (man-to-snail versus snail-to-man), for arbitrary worm aggregation; the relation between Rosenfield's [30] empirical work and more abstract models.

INTRODUCTION

Human schistosomiasis is a parasitic infection which has been estimated to afflict about 200 million people, or 1 in every 20 people in the world. This includes maybe 100,000 Puerto Rican immigrants in New York City. The infection is primarily caused by one or other of three species of flatworms, each of which has a life cycle involving a sexual stage in the definitive host (man), and an asexual stage in an intermediate host (specific snails). The detailed dynamics of the infection are exceedingly complex, because both the transmission stages from people to snails (via miracidiae developed from eggs excreted into water) and from snails to people (via cercariae shed by

infected snails into the water) involve all manner of sociological and geographical complications: for example, patterns of human contact with water, both for passing eggs and for exposure to cercariae, are likely to depend significantly on people's ages and on the geographical relation of a settlement to its local streams and ponds.

Despite this acknowledged complexity, simple mathematical models can be useful in illuminating qualitative aspects of the overall dynamics of the disease. In particular, MacDonald [22] has emphasized that the presence of two sexes of the parasite in the definitive host has important implications for the transmission dynamics, leading to features (e.g., the so-called "breakpoint") which are not found in diseases such as malaria, and which may have significance for public health policies.

The present paper examines the effects produced by some qualitative alterations to the basic models of MacDonald and later workers. These alterations are in the direction of making the models somewhat more realistic.

In the work by MacDonald and its subsequent refinements and elaborations (e.g., [25–28, 18]), adult schistosomes are assumed to be independently randomly distributed among the human hosts; this gives a Poisson distribution for the number of schistosomes per person. Subsequent calculations of the fraction of worms that are paired, and thus egg-producing, are based on this assumption. But there are theoretical arguments and empirical evidence which suggest that schistosomes are not independently randomly distributed, but rather are distributed in a clumped or "contagious" fashion. Such clumping of worms can have a significant effect on the fraction of worms expected to be paired, and thence a qualitative effect on the transmission dynamics.

The *first* thing this paper does is to present a way of characterizing clumped worm distributions, both when the two sexes are aggregated together ("case I") and when they are aggregated separately ("case II"): this is done in Sec. 1. The probability for a given person to have one or more worms ("prevalence of worms", W), the probability for one or more worm pairs ("prevalence of pairs", Ω), and the probability for a given worm to be mated ("mating probability", ϕ) are then calculated as functions of the average worm load per person, m, and of the degree of clumping, for case I in Sec. 2 and for case II in Sec. 3. The consequent relationships between prevalence of worms, prevalence of pairs, and average egg output per person are explored in Sec. 4: these relationships are in principle susceptible to confrontation with medical data.

Second, in Sec. 5, the MacDonald-Nasell-Hirsch (hereafter MNH) analysis of the transmission dynamics is generalized, so that the results depend on the type (sexes together or separate) and degree of worm clumping. The MNH results for independently randomly distributed worms are now a

limiting case. The implications for the threshold and breakpoint phenomena are discussed in Sec. 6.

Third, Sec. 7 indicates how, without significant extra complication, the analysis may be made more realistic by allowing for a latent period between the moment when a snail is infected (by a miracidium) and the moment it begins shedding cercariae. Previous studies have either omitted such a latent period, or have described it by "catalytic" models (with a transition rate through the latent phase, rather than a precise latent period of T days) in a rather complicated formal analysis [26] or in computer simulations [19]. It is seen that inclusion of such a latent period allows high worm loads in man to be reconciled with snail populations in which only a small fraction of snails are shedding cercariae. This is often the case in nature [34], but is not explained by the conventional MNH models.

Various minor points are made. Aspects of the dynamical relationships among the more detailed Nasell-Hirsch model (with two simultaneous differential equations for mean worm load, m, and fraction of snails infected), the MacDonald model (with one differential equation, for m), and the phenomenological work of Rosenfield [30, 31] are discussed in Sec. 5: the relations hinge on the relative magnitudes of relevant time scales. Throughout the main text, the worms are taken to be monogamous; the consequences of a promiscuous mating system are outlined in Appendix C.

The above work on the overall transmission cycle follows previous studies in dealing with aggregated populations of humans and of snails, both of which are assumed constant over the time scales of relevance to the transmission dynamics. Complications arising from age-specific differences in contact rates and recovery rates, or from ecological fluctuations in snail abundance, are ignored. So are the details of inhomogeneities in egg dispersal, of the way miracidiae "find" snails, and of the way cercariae "find" people. For excellent analytic reviews of some of the recent work on these topics, see Cohen [7, 8] and Fine [12].

The prime motive in the present work is to help improve our understanding of qualitative features of the transmission dynamics of schistosomiasis and other similar parasitic infections. To this end, the basic biological assumptions going into the models (and the empirical evidence supporting these assumptions), along with the conclusions and implications for public-health policies, are presented in the medical literature (Bradley and May, [4]; hereafter BM). As befits a paper addressed to public-health workers and epidemiologists, BM relies heavily on descriptive, graphical, and interpretive accounts of the assumptions and conclusions; the intervening mathematical details are entirely omitted. The present paper complements BM by supplying the mathematics. It both underpins BM and serves as a point of departure for further empirical work (particularly Secs. 4 and 7). Conversely, in the present crowded state of the literature, duplication is to be

avoided, and consequently the present paper is largely *confined* to the mathematical development of the models: formative data and practical tests and applications are touched on but briefly (although with appropriate references).

The discussion in this paper, and in BM, is largely developed within the specific context of schistosomiasis. It is to be emphasized that most of the dynamical features of these models apply to a large class of other parasitic infections, where the adult parasite has a sexual stage in the primary host. The various filarial parasites, estimated to afflict about 300 million people, are of this kind; indeed, the simple models may be somewhat more realistic here, as the vectors are mainly mosquitos and blackflies whose activities are more uniformly spread over geographical space and over age classes than are the activities of cercarial-shedding snails (K. Dietz, private communication). One of the nastiest of human diseases is of this kind: onchocerciasis or river blindness, transmitted by the fly *Simulium damnosum*, and infecting more than a million people in the upper basin of the Volta river alone.

1. CLUMPED WORM DISTRIBUTIONS: THE NEGATIVE BINOMIAL

In BM there is reviewed a body of empirical evidence and theoretical argument suggesting that adult schistosomes are not independently randomly distributed in their human hosts, but rather are distributed in a clumped or overdispersed way.

We use the negative binomial to describe such overdispersed distributions. As reviewed in BM, this family of distributions arises from various plausible models of the ecology of the transmission process (e.g., [2, 33]; K. Dietz, private communication), and it is in accord with published data on helminthic infections in animals (e.g., [32]). Our basic justification for its use is, however, frankly phenomenological: the negative binomial distribution provides a 1-parameter characterization of the degree of overdispersion, in terms of a parameter k (the smaller k, the more overdispersed the distribution).

Specifically, the probability for a given person to have n worms is then (ignoring for the moment the complications introduced by having two sexes of worms)

$$P(n|m,k) = (1-\alpha)^k \frac{\Gamma(k+n)}{\Gamma(k)} \frac{\alpha^n}{n!}. \tag{1.1}$$

Here m is the mean worm load per person, k is the clumping parameter, and $\Gamma(z)$ is the gamma function (e.g., Abramowitz and Stegun (henceforth

AS), [1], Chapter 6). For notational convenience, α is defined as

$$\alpha = \frac{m}{m+k}. \tag{1.2}$$

Equivalently, the distribution is defined by the generating function

$$g(z) = (1-\alpha)^k (1-\alpha z)^{-k}. \tag{1.3}$$

For further discussion, see e.g., [29].

Some limiting cases are to be noted. In the limit $k \to \infty$, the Poisson distribution is recovered, corresponding to the worms being independently randomly distributed. For integer k, the distribution (1.1) is relatively tractable. For $k = 1$, the distribution becomes a geometric series. In the limit $k \to 0$, all hosts, except a fraction of order k, have zero worms; the mean load m is maintained by a small fraction of order k having loads of order m/k. In this limit $k \to 0$, with the zero class removed one gets a logseries distribution [13, 36].

In the subsequent discussion, we will be particularly concerned with the way the worm distribution affects the probability that a given female will be mated, and thus by assumption producing eggs. Several biological and mathematical assumptions underly this discussion. We confine attention to the equilibrium situation, and disregard complications attendant upon the sequential input of worms or upon the death of one partner: such complications at worst introduce factor-of-2 effects (see, e.g., [10]). The sex ratio is taken to be unity. Throughout the main part of the paper, the worms are assumed to have a monogamous mating system, and furthermore it is assumed that all potential pairs do indeed find each other inside the host. Thus in a host with i female and j male worms, the number of egg-producing females is the lesser of i and j. In the Appendix C we analyze the extreme opposite mating system of complete promiscuity (in which the number of egg-producing females is i if $j \geqslant 1$, and zero otherwise); again, the type of mating systems is seen to make for quantitative rather than qualitative corrections. All these assumptions are reviewed more fully in BM.

The one question that does exert a qualitative influence on the dynamics is whether the two sexes are distributed together or separately. One extreme assumption, which hereafter will be referred to as *case I*, or "together", is that females and males are distributed together in a single negative binomial distribution (with mean m and clumping parameter k), each individual worm being female or male with probability $\frac{1}{2}$. The opposite extreme, referred to as *case II*, or "separate", is that the female worms are distributed in a negative binomial (with mean $m/2$ and parameter k), and the males are distributed separately in their own negative binomial distribution (also with

a mean $m/2$ and parameter k). As discussed more fully in BM, case I is likely to apply at high worm densities, while case II may be plausible at low densities; the reality may well be some m-dependent blend.

Throughout the following sections, subscripts t are used to denote case I, sexes distributed together, and subscripts s to denote case II, sexes distributed separately.

2. PAIRING PROBABILITY: CASE I (FEMALE AND MALE DISTRIBUTED TOGETHER)

In this case, the probability for a given host to have i female and j male worms is

$$\mathbf{P}_t(i,j|m,k)=(1-\alpha)^k\frac{\Gamma(i+j+k)}{\Gamma(k)}\frac{(\alpha/2)^{i+j}}{i!j!}. \tag{2.1}$$

As always, m is the mean worm load (disregarding sexes), k is the aggregation parameter, and α is defined by Eq. (1.2). Given that male and female worms are distributed together, the probability of having a total of $i+j$ worms is given by Eq. (1.1) with $n=i+j$; given that each worm is equally likely to be female or male, the probability that the $i+j$ worms comprise exactly i females and j males is $2^{-i-j}(i+j)!/(i!j!)$: hence Eq. (2.1).

The pair distribution function, $\Pi(j|m,k)$, gives the probability for a given host to contain exactly j female-male pairs. From Eq. (2.1) we have

$$\Pi_t(j|m,k)=\sum_{i=j}^{\infty}\theta_{ij}\mathbf{P}_t(i,j|m,k). \tag{2.2}$$

Here $\theta_{ij}=1$ if $i=j$, and $\theta_{ij}=2$ otherwise: this factor arises because j pairs may be realized either by an excess of females or by an excess of males, thus producing a counting factor of 2 (unless $i=j$). Substituting Eq. (2.1) into (2.2) and writing $l=i-j$, we get

$$\Pi_t(j|m,k)=\frac{(1-\alpha)^k}{\Gamma(k)j!}\sum_{l=0}^{\infty}\theta_{l0}\frac{\Gamma(k+2j+l)}{\Gamma(j+1+l)}\left(\frac{\alpha}{2}\right)^{2j+l}. \tag{2.3}$$

That is,

$$\Pi_t(j|m,k)=(1-\alpha)^k\frac{\Gamma(k+2j)}{\Gamma(k)}\frac{(\alpha/2)^{2j}}{j!j!}\left[2F(k+2j,1|j+1|\alpha/2)-1\right]. \tag{2.4}$$

Here $F(a,b|c|z)$ is the hypergeometric function (AS, Chapter 15). An equivalent result has been obtained by Leyton [20]. In the Poisson limit of

independently randomly distributed worms, $k \to \infty$, the appropriate limiting form of Eq. (2.1) may be substituted directly into Eq. (2.2) to get [20]

$$\Pi_t(j|m,k\to\infty) = e^{-m}\frac{(m/2)^j}{j!}\sum_{i=j}^{\infty}\theta_{ij}\frac{(m/2)^i}{i!}. \tag{2.5}$$

For the opposite limit of a highly overdispersed distribution, $k \to 0$, Eq. (2.4) gives for the zero-pair class

$$\Pi_t(0|m,k\to 0) = 1 - O(k). \tag{2.6}$$

For $j \neq 0$, we use AS formula 15-1-24 and the duplication formula for the gamma function (AS 6-1-18), to get

$$\Pi_t(j|m,k\to 0) \approx \frac{k}{j}\left[1 - \frac{\Gamma\left(j+\frac{1}{2}\right)}{2\Gamma\left(\frac{1}{2}\right)j!}\right], \tag{2.7}$$

where terms of order k^2 have been neglected.

If it is assumed that the egg output per person is proportional to the number of mated females, the above results give the distribution of egg output in the host community. The pair distributions are discussed in this light, as functions of m and k, by Gliddon and Bradley [14], who compare them with some data and with MacDonald's [23] earlier discussion.

We now proceed to give expressions for: (i) the prevalence of worms; (ii) the prevalence of pairs; and (iii) the mating probability. After presenting the general formulae, we catalogue various limiting cases.

(i) *The prevalence of worms*, W, is defined to be the probability that a given member of the host population will harbor one or more worms. Clearly W is given in general by

$$W(m,k) = 1 - \mathbf{P}(0,0|m,k). \tag{2.8}$$

Substituting from Eq. (2.1) for case I, where females and males are distributed together, we have

$$W_t(m,k) = 1 - (1-\alpha)^k. \tag{2.9}$$

Using Eq. (1.2), this takes the form

$$W_t(m,k) = 1 - (1+m/k)^{-k}. \tag{2.10}$$

(ii) *The prevalence of pairs*, Ω, is defined to be the probability for a host to have one or more female-male pairs. For case I, this is most conveniently

calculated by observing that hosts with no such pairs occur either because there are no worms present, or because all worms are of the same sex (an event which has probability 2^{1-n} if n worms are present). That is, referring back to Eq. (1.1) for the overall probability to have n worms regardless of sex,

$$1-\Omega_t = \mathbf{P}_t(0,0|m,k) + \sum_{n=1}^{\infty} P(n|m,k)2^{1-n}. \tag{2.11}$$

Thus

$$\Omega_t(m,k) = 1 - 2\sum_{n=0}^{\infty} P(n|m,k)2^{-n} + (1-\alpha)^k. \tag{2.12}$$

By use of the generating function given in Eq. (1.3), the sum here can be seen to have the value $(1-\alpha)^k(1-\alpha/2)^{-k}$. Using Eq. (1.2) to express α in terms of m and k, this leads to

$$\Omega_t(m,k) = 1 - 2\left(1+\frac{m}{2k}\right)^{-k} + \left(1+\frac{m}{k}\right)^{-k}. \tag{2.13}$$

(iii) We define the *mating probability* ϕ as the probability that a given female will be mated, and thus (by assumption) producing eggs. For a monogamous mating system, as assumed throughout the main part of the paper, ϕ corresponds to the probability that a given worm will be paired; for $k\to\infty$, ϕ is MacDonald's [22] α. A related quantity is the total number of paired worms per person, ψ [25], which for monogamous worms is obviously related to ϕ by

$$\psi(m,k) = m\phi(m,k). \tag{2.14}$$

The calculation of $\phi_t(m,k)$ for case I is carried out in Appendix A:

$$\phi_t(m,k) = 1 - \frac{(1-\alpha)^{1+k}}{2\pi}\int_0^{2\pi} \frac{(1-\cos\theta)\,d\theta}{(1+\alpha\cos\theta)^{1+k}}. \tag{2.15}$$

Equivalent expressions can be obtained in terms of hypergeometric functions, or of generalized Legendre functions; these are indicated in Appendix A. The formula (2.15) is, however, a convenient one, which lends itself readily to the calculation of limiting results for large and small m and k. For integer values of k, the integral in Eq. (2.15) can easily be evaluated by contour integration, to give algebraic expressions for ϕ_t; for half-odd-integer values of k, the integral can be expressed in terms of relatively familiar elliptic integrals.

The expressions for W_t, Ω_t, and ϕ_t are now given explicitly for the interesting special cases $k\to\infty$, $k=1$, and $k\to 0$. Limiting results for small and large m are also listed.

For the limit $k\to\infty$, the asymptotic result

$$\lim_{k\to\infty}\left(1+\frac{x}{k}\right)^k = e^x \tag{2.16}$$

may be used in Eqs. (2.10), (2.13), and (2.15) to give the formulae for individually randomly distributed worms that are well known from the work of MacDonald [22] and Nasell and Hirsch [25]. For the prevalence of worms and of pairs, Eqs. (2.10) and (2.13) respectively become

$$W_t(m,k\to\infty) = 1-e^{-m}, \tag{2.17}$$

$$\Omega_t(m,k\to\infty) = (1-e^{-m/2})^2. \tag{2.18}$$

The mating probability follows from the limiting form of Eq. (2.15), which (as shown in Appendix A) is

$$\phi_t(m,k\to\infty) = 1-e^{-m}[I_0(m)+I_1(m)]. \tag{2.19}$$

For $k=1$, Eqs. (2.10) and (2.13) give

$$W_t(m,1) = \frac{m}{1+m}, \tag{2.20}$$

$$\Omega_t(m,1) = \frac{m^2}{(1+m)(2+m)}. \tag{2.21}$$

The integral in Eq. (2.15) is routine for $k=1$, and leads to

$$\phi_t(m,1) = 1-(1+2m)^{-1/2}. \tag{2.22}$$

For the limit $k\to 0$, we may neglect terms of order k^2 to write x^k as $1+k\ln x$. This leads to the approximations

$$W_t(m,k\to 0) = k\ln(1+m/k)+O(k^2), \tag{2.23}$$

$$\Omega_t(m,k\to 0) = k\ln\left[\frac{(m+2k)^2}{4k(m+k)}\right]+O(k^2). \tag{2.24}$$

For Eq. (2.15) in the limit $k\to 0$, it is shown in Appendix A that

$$\phi_t(m,k\to 0) = 1-\left[\frac{1-\alpha}{\alpha}\right]\left[\left(\frac{1+\alpha}{1-\alpha}\right)^{1/2}-1\right][1+O(k)], \tag{2.25}$$

with α as always given by Eq. (1.2). Unless m is so small as to be comparable with k, this expression for the mating probability reduces to

$$\phi_t(m,k\to 0)\approx 1-(2k/m)^{1/2}+O(k/m). \tag{2.26}$$

For small m (which, as shown below, essentially means for $m<k/[1+k]$), we have the further useful results from Eqs. (2.10) and (2.13):

$$W_t(m,k)=m\left[1-\frac{m(1+k)}{2k}+\cdots\right], \tag{2.27}$$

$$\Omega_t(m,k)=\frac{m^2(1+k)}{4k}\left[1-\frac{m(2+k)}{2k}+\cdots\right]. \tag{2.28}$$

For small m (small α) the denominator in the integrand in Eq. (2.15) may be expanded in a power series, leading to

$$\phi_t(m,k)=\frac{m}{2}\left(\frac{1+k}{k}\right)\left[1-\frac{m(2+k)}{2k}+\cdots\right]. \tag{2.29}$$

For large m (which essentially means for $m>k$), Eqs. (2.10) and (2.13) have the obvious limiting forms

$$W_t(m,k)=1-(k/m)^k+\cdots, \tag{2.30}$$

$$\Omega_t(m,k)=1-(2^{1+k}-1)(k/m)^k+\cdots. \tag{2.31}$$

The asymptotic form of ϕ_t for large m is less trivial. As shown in Appendix A, it is

$$\phi_t(m,k)=1-\frac{c(k)}{\sqrt{m}}+O\left(\frac{k}{m}\right), \tag{2.32}$$

with $c(k)$ defined by

$$c(k)=\left(\frac{2k}{\pi}\right)^{1/2}\frac{\Gamma\left(k+\frac{1}{2}\right)}{\Gamma(k+1)}. \tag{2.33}$$

In particular, $c(\infty)=\sqrt{2/\pi}$, $c(1)=1/\sqrt{2}$, and $c(k\to 0)=\sqrt{2k}$, which provide independent checks on Eqs. (2.19), (2.22), and (2.26) respectively.

The pairing probability $\phi_t(m,k)$ is displayed as a function of mean worm load m, for various k, in Fig. 1. All the trends manifested in this figure, and by the other quantities discussed in this section, are susceptible to intuitive explanation. Such ratiocination is presented at length in BM.

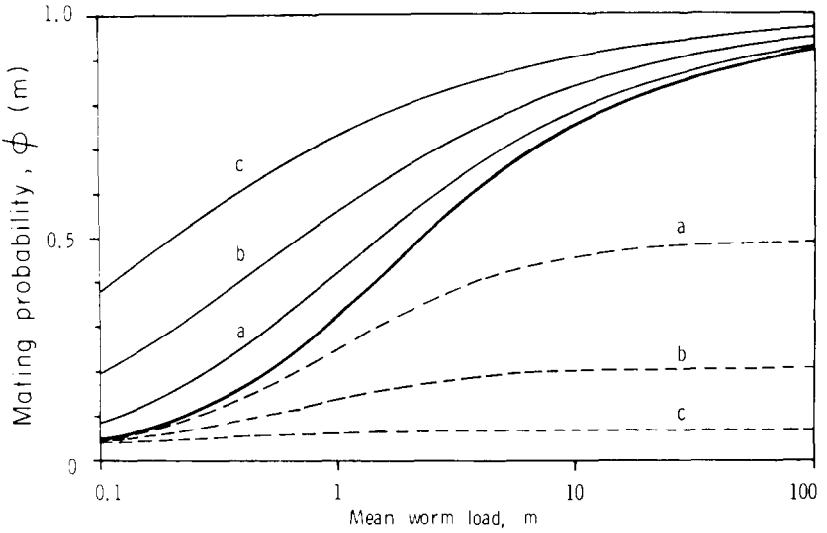

FIG. 1. The probability ϕ that a given female worm is mated (assumed equivalent to the pairing probability in a monagamous mating system), as a function of the mean worm load per person, m, for various assumptions about the worm distribution function. The thick solid line is the "reference" case of independently randomly distributed worms (i.e., a Poisson distribution). The thin solid lines pertain to case I, where female and male worms are distributed together according to a negative binomial with parameter k; the dashed lines are for case II, where female and male worms are distributed in separate negative binomials, each with parameter k. In either case, the curve labeled (a) is for $k=1$ (geometric series distribution), (b) for $k=0.2$, (c) for $k=0.05$.

3. PAIRING PROBABILITY: CASE II (FEMALES AND MALES DISTRIBUTED SEPARATELY)

In this case, the female worms are distributed according to a negative binomial with mean $m/2$ and parameter k, and the male worms are distributed in their own separate negative binomial, also with mean $m/2$ and parameter k. Consequently the probability for a given host to have exactly i female and j male worms is

$$\mathbf{P}_s(i,j|m,k) = P(i|m/2,k)P(j|m/2,k). \tag{3.1}$$

The negative binomial distributions on the RHS are as given in Eq. (1.1), whence

$$\mathbf{P}_s(i,j|m,k) = (1-\alpha')^{2k}\frac{\Gamma(i+k)\Gamma(j+k)}{\Gamma(k)\Gamma(k)i!j!}(\alpha')^{i+j}. \tag{3.2}$$

For notational convenience, α' is defined [from Eq. (1.2), the mean being $m/2$] as

$$\alpha' = \frac{m}{m+2k}. \tag{3.3}$$

The pair distribution function, $\Pi_s(j|m,k)$, for the probability of a host to have exactly j female-male pairs follows from Eq. (2.2). For case II this gives

$$\Pi_s(j|m,k) = P(j|m/2,k) \sum_{i=j}^{\infty} \theta_{ij} P(i|m/2,k). \tag{3.4}$$

Here the function θ_{ij} is as defined below Eq. (2.2).

In the limit $k \to \infty$, Eq. (3.4) clearly reduces to Eq. (2.5) of the preceding section. This is the formal mathematical expression of the fact that when the worms are all independently randomly distributed, the distinction between whether the two sexes are distributed together or separately is lost; in the limit $k \to \infty$, case I and case II coalesce.

We now parallel the presentation in Sec. 2, first giving general formulae for W, Ω, and ϕ, and then cataloguing various special cases.

(i) *The prevalence of worms*, W, is given by Eq. (2.8). For case II, it is simply the complement of the probability that an individual host has neither a female nor a male worm:

$$W_s(m,k) = 1 - \left[P(0|m/2,k) \right]^2. \tag{3.5}$$

Here $P(0|m/2,k)$ is given by the negative binomial (1.1), but in fact Eq. (3.5) applies quite generally for case II, regardless of the specific distributions of female and of male worms. Substituting from Eq. (1.1), we have

$$W_s(m,k) = 1 - \left(1 + \frac{m}{2k}\right)^{-2k}. \tag{3.6}$$

(ii) *The prevalence of pairs*, Ω_s, for case II is simply the product of the probability that there is one or more female and the probability that there is one or more male worm:

$$\Omega_s(m,k) = \left[1 - P(0|m/2,k) \right]^2. \tag{3.7}$$

Again, this expression applies generally, regardless of the particular distribution functions for female and for male worms. Substituting from Eq. (1.1)

gives

$$\Omega_s(m,k)=\left[1-\left(1+\frac{m}{2k}\right)^{-k}\right]^2. \tag{3.8}$$

As is also true in Sec. 2, this result could alternatively be obtained directly from the zero class of the pair distribution, as given by Eq. (3.4): the above method is simpler.

(iii) The *mating probability* ϕ corresponds to the pairing probability under the assumption of monogamy. With ψ, as before, defined as the total number of paired worms, we have

$$\psi_s(m,k)=\sum_{j=0}^{\infty} 2j\Pi_s(j|m,k). \tag{3.9}$$

Substituting from Eq. (1.1) into Eq. (3.4), and thence into Eq. (3.9), we rearrange the order of summation to get

$$\psi_s(m,k)=2(1-\alpha')^{2k}\sum_{i=0}^{\infty}\sum_{j=0}^{i} j\theta_{ij}\frac{\Gamma(i+k)\Gamma(j+k)}{\Gamma(k)\Gamma(k)i!j!}(\alpha')^{i+j}. \tag{3.10}$$

Here α' is defined by Eq. (3.3). In conjunction with the relation (2.14), $\psi=m\phi$, this gives $\phi_s(m,k)$. I have not been able to reduce the general expression (3.10) to any simpler closed form [analogous, e.g., to Eq. (2.15) for case I]. I have obtained analytic results for $k=1$ and $k\to 0$; these are given below. The relation between $\phi_s(m)$ and m is shown for some other values of k in Fig. 1; these results were obtained from Eq. (3.10) by numerical computation.

For the limit $k\to\infty$, we recover the Poisson distribution results, for the reason discussed above. W_s, Ω_s, and ϕ_s in this limit are therefore given by Eqs. (2.17), (2.18), and (2.19) respectively.

For $k=1$, Eqs. (3.6) and (3.8) become

$$W_s(m,1)=m(m+4)/(m+2)^2, \tag{3.11}$$

$$\Omega_s(m,1)=m^2/(m+2)^2. \tag{3.12}$$

As shown in Appendix B, the pairing probability, from Eq. (3.10), simplifies to

$$\phi_s(m,1)=\frac{m}{2(1+m)}. \tag{3.13}$$

In the limit $k \to 0$, both female and male worm distributions are highly clumped, and the appropriate limiting expressions for Eqs. (3.6) and (3.8) are

$$W_s(m, k \to 0) = 2k \ln\left(1 + \frac{m}{2k}\right) + O(k^2), \tag{3.14}$$

$$\Omega_s(m, k \to 0) = k^2 \left[\ln(1 + m/2k)\right]^2 + O(k^3). \tag{3.15}$$

The mating probability in this limit may be expressed as (see Appendix B)

$$\phi_s(m, k \to 0) = \frac{k}{\alpha'}\left[(1+\alpha')\ln(1+\alpha') + (1-\alpha')\ln(1-\alpha')\right]\left[1 + O(k)\right]. \tag{3.16}$$

Here, as usual, α' is defined by Eq. (3.3). Unless m is so small as to be comparable with k, Eq. (3.16) reduces to

$$\phi_s(m, k \to 0) \approx k(2 \ln 2) + O(k^2 \ln k). \tag{3.17}$$

For small m (which, as seen immediately below, means for $m < k/[1 + k]$), Eqs. (3.6), (3.8), and (3.10) are approximated by

$$W_s(m, k) = m\left[1 - \frac{m(1+2k)}{4k} + \cdots\right], \tag{3.18}$$

$$\Omega_s(m, k) = \frac{m^2}{4}\left[1 - \frac{m(1+k)}{2k} + \cdots\right], \tag{3.19}$$

$$\phi_s(m, k) = \tfrac{1}{2}m\left[1 - \frac{m(1+k)}{2k} + \cdots\right]. \tag{3.20}$$

For large m (which essentially means for $m > k$), Eqs. (3.6) and (3.8) have the obvious limiting forms

$$W_s(m, k) = 1 - (2k/m)^{2k} + \cdots, \tag{3.21}$$

$$\Omega_s(m, k) = 1 - 2(2k/m)^k + \cdots. \tag{3.22}$$

The mating or pairing probability settles asymptotically to a constant value, less than unity:

$$\phi_s(m, k) = \kappa(k) + O(k/m). \tag{3.23}$$

This result is obtained in Appendix B, where it is shown that κ is the

constant

$$\kappa(k) = 1 - \frac{\Gamma\left(k+\frac{1}{2}\right)}{\Gamma\left(\frac{1}{2}\right)\Gamma(k+1)}. \tag{3.24}$$

In particular, $\kappa(\infty)=1$, $\kappa(1)=\frac{1}{2}$, and $\kappa(k\to 0)=2k\ln 2$, in accord with the results given above for these values of k.

The general trends manifested by the mating probability $\phi_s(m,k)$ as a function of m, for various k, are displayed in Fig. 1. Qualitative explanations of these trends, and in particular of why ϕ_s does not saturate to unity at high worm loads, are given in BM.

4. PREVALENCE OF WORMS, OF PAIRS, AND TOTAL EGG OUTPUT

As mentioned earlier, if it is assumed that the egg output is directly proportional to the number of mated females within the host (a debatable assumption), then the pairing distributions [Eq. (2.4) or (3.4)] give the distribution of egg output in the host community.

In dealing with W, Ω, or ψ, one is dealing with single numbers rather than with the full distribution function for worms. The corresponding advantage is that each of these single numbers is, in principle, relatively easy to estimate. The prevalence of worms, W, may be estimated from skin antigen tests (see, e.g., [7, 15]). The prevalence of pairs, Ω, may for monogamous worms be estimated from the fraction of the host population excreting eggs. And ψ, the mean number of paired worms per person, may be estimated from the mean egg output per person (under the assumption noted in the preceding paragraph). There are practical difficulties in estimating any of these quantities (see, e.g., [17]), and further difficulties in comparing estimated magnitudes for different age classes within a community, not to mention between communities. Some of these problems are discussed in BM and in [12]. Nevertheless, the patterns of relationship among W, Ω, and ψ are interesting, and have potential applications as indirect tests for the underlying worm distribution function.

(i) *The relation between W and Ω* is simple if female and male worms are distributed separately. As may be seen from Eqs. (3.5) and (3.7), the relation

$$\Omega_s = \left(1 - \sqrt{1 - W_s}\right)^2 \tag{4.1}$$

holds for case II regardless of the specific distribution functions for female and for male worms (so long as they be the same), and regardless of the degree of aggregation for female and male worms. That is, there is a

"universal" relation (4.1) between W and Ω if case II pertains; this relation is necessarily congruent with the Poisson one for completely independently distributed worms.

For case I, where females and males are distributed together, the relation between W and Ω depends upon the assumed distribution function, and thence, for the negative binomial, upon k. Juggling Eqs. (2.10) and (2.13), we get

$$\Omega_t = 2 - W_t - 2^{1+k}(1 - W_t)\left[1 + (1 - W_t)^{1/k}\right]^{-k}. \tag{4.2}$$

In the limit $k \to \infty$, this reduces to Eq. (4.1).

The relations (4.1) and (4.2) are displayed graphically in BM, and some of the implications and possible applications are discussed.

(ii) *The relations between W and ψ, and between Ω and ψ*, also have potential practical usefulness. Such relations may be obtained by treating m as an implicit variable, to plot, for example, W from Eq. (2.10) or (3.6) against ψ from Eq. (2.15) or (3.10), for various specified values of k. Using the equations derived above, the results of such computations are illustrated, and their implications discussed, in BM.

5. TRANSMISSION DYNAMICS OF SCHISTOSOMIASIS

We now turn to the overall transmission dynamics of schistosomiasis and other similar helminthic infections, paying particular attention to the dependence upon the pattern of aggregation of female and male worms in their primary hosts. In essence, we extend the classic work of MNH, replacing their mating function $\phi(m, \infty)$ for a Poisson distribution of independently randomly distributed worms by the more general $\phi_t(m,k)$ or $\phi_s(m,k)$, as given by Eq. (2.15) or (3.10) respectively.

Following MNH, we assume that the total number of human hosts, N_1, and that of snails, N_2, are constants. For the human population, this is a reasonable approximation; for the snail population, it is a more dubious assumption. The two dynamical variables of interest are then $m(t)$, the average number of worms per human host, and $y(t)$, the fraction of the snail population which is shedding cercariae, both as functions of time t.

For $m(t)$ we have the equation [25–28]

$$\frac{dm}{dt} = \mu_1[T_1 y - m]. \tag{5.1}$$

The mean worm load per person is in dynamical balance between forces of infection and of worm death: μ_1 is the death rate for mature schistosomes, and T_1 is the quantity defined by Nasell and Hirsch [25] which characterizes the transmission of parasites *from snail to man*. More specifically, $T_1 =$

$N_2\lambda_2 p_1/\mu_1$, with λ_2 the rate of cercarial shedding per infected snail, p_1 the probability for a cercaria to infect a given human, and N_2 and μ_1 as above.

Similarly, $y(t)$ is in balance between forces of infection and snail death:

$$\frac{dy}{dt} = h_2(1-y) - \mu_2 y. \tag{5.2}$$

Here μ_2 is the snail death rate (see discussion in BM), and h_2 the infection rate per snail. Defining p_2 as the probability for an egg to infect a given snail, λ_1 as the rate of egg laying per mated female, and N_1 as above, and remembering that $\frac{1}{2}m\phi(m,k)$ is the average number of mated females per host, we have

$$h_2 = \tfrac{1}{2}N_1 p_2 \lambda_1 m\phi. \tag{5.3}$$

Following Nasell and Hirsch's definition of T_2 as the combination of parameters which characterizes the transmission of parasites *from man to snail*, $T_2 = N_1\lambda_1 p_2/\mu_2$, we then have

$$\frac{dy}{dt} = \mu_2\left[\tfrac{1}{2}T_2 m\phi(1-y) - y\right]. \tag{5.4}$$

The basic equations (5.1) and (5.4) are those derived, with a much fuller discussion, by Nasell and Hirsch [25] and Nasell [26, 27]. The difference is that the general mating probability $\phi(m,k)$ has replaced their $\phi(m,\infty)$ for Poisson-distributed worms.

Two further assumptions implicit in Eqs. (5.1) and (5.4) are: (i) that the human hosts exhibit no immune responses or other density-dependent effects which would tend to increase the worm death rate, or decrease the infection rate, at high values of m; and (ii) that the rate of egg production is independent of the number of egg-producing females in a host. The essential mechanism which prevents the system "running away" to unboundedly large values of m lies in the equation for $y(t)$: snails can only be infected once (whence the factor $1-y$); a second infection does not increase the output of cercariae. In jargon terms, there is no "superinfection" of snails. The qualitative effect of relaxing the assumptions (i) and (ii) will be discussed at the end of Sec. 6.

An analytic solution of Eqs. (5.1) and (5.4) for arbitrary ϕ is not feasible. The qualitative dynamical behavior can, however, be laid bare. For given y, the mean worm load is stationary ($dm/dt = 0$) along the osocline

$$m = T_1 y; \tag{5.5}$$

for larger m, $dm/dt < 0$, and for smaller m, $dm/dt > 0$. Similarly, for given

m, y is stationary ($dy/dt = 0$) along the isocline

$$y = \frac{\frac{1}{2}T_2 m\phi}{1 + \frac{1}{2}T_2 m\phi}; \tag{5.6}$$

for larger y, $dy/dt < 0$, and for smaller y, $dy/dt > 0$.

Once these two isoclines are constructed on the y-m plane, it can be seen in what directions the dynamical trajectories move in the various regions on this plane. Two cases can be quite generally distinguished. In the first, illustrated by Fig. 2, the two isoclines intersect only at the origin, and all trajectories are attracted to $m = 0, y = 0$: the infection cannot maintain itself. In the second, illustrated by Fig. 3, there are 3 points of intersection of the isoclines, corresponding to 2 stable points (at $m = 0$ and at $m = m^*$), divided by an unstable point (at $m = m_B$). The directions of the trajectories in the various regions are clear: points (i.e., initial values of m and y) originating to the left of the dashed line which passes through m_B are attracted to the

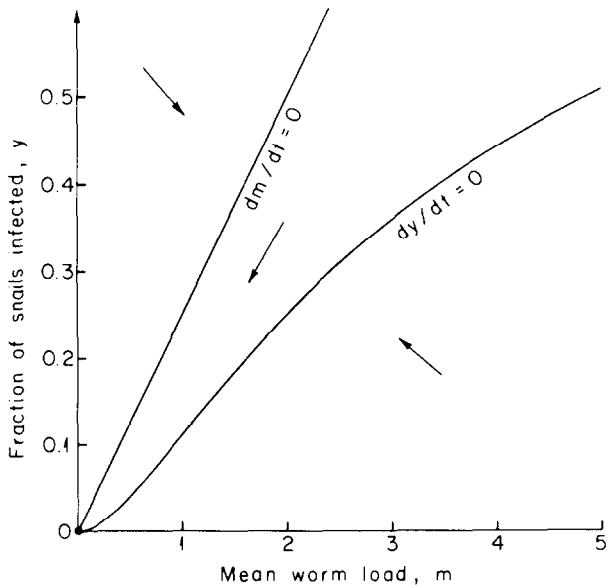

FIG. 2. The arrows indicate how the dynamical trajectories of $y(t)$ and $m(t)$ behave in the various regions into which the y-m plane is dissected by the isoclines $dy/dt = 0$ and $dm/dt = 0$. The figure corresponds to transmission coefficients below threshold, when the infection cannot maintain itself, and all trajectories are attracted to the origin. This specific illustration is for case II (sexes distributed separately) with $k = 1$, $T_1 = 4$, and $T_2 = 1$; Eq. (6.9) shows this to be below threshold.

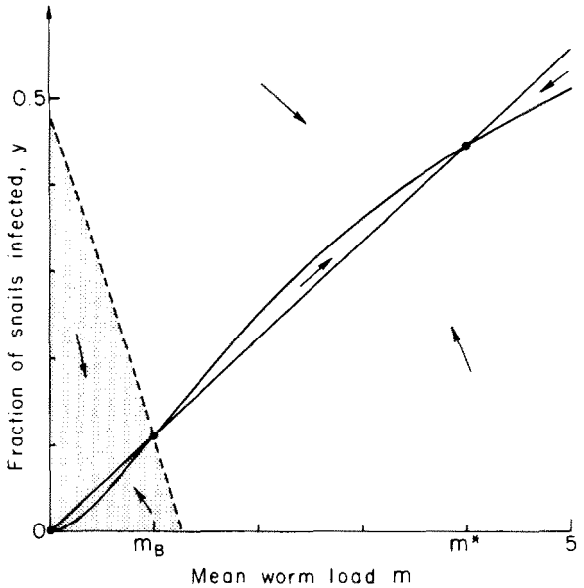

FIG. 3. Same as in Fig. 2 (case II, $k=1$), except that here $T_1=9$ and $T_2=1$. The system is now above threshold, and there are two alternative stable states (one at m^*, one at the origin), each with its own domain of attraction. The boundary between the two regions depends on the ratio μ_2/μ_1, here taken to be 3; points in the shaded region are attracted to the origin, points outside to m^*. In the limit $\mu_2 \gg \mu_1$, this boundary becomes a vertical line through the unstable point m_B, and we can speak of *the* breakpoint at a worm load m_B. (See also [25, 27)].

origin; points originating to the right of the dashed line are attracted to the point m^* at which the infection maintains itself in stable equilibrium.

The generic case illustrated by Fig. 2 corresponds to the transmission parameters being below "threshold". The generic case illustrated by Fig. 3 corresponds to parameters above threshold, and in this event there are two alternate stable configurations (one at $y=0$, $m=0$ and one at a finite value of y^*, m^*). The dashed line divides the y-m plane into the 2 points' respective domains of attraction; the particular value m_B is sometimes referred to as the "breakpoint" [22].

The details of the threshold and breakpoint phenomena, and of the dashed domain-dividing line in Fig. 3, depend upon the values of T_1 and T_2, and on the clumping parameter k (for either case I or case II). The case $k \to \infty$ has been discussed thoroughly by Nasell and Hirsch [25] and Nasell [27, 28].

Before pursuing the threshold and breakpoint criteria in detail (Sec. 6), we make some further general comments about the dynamics of the system.

From Eqs. (5.1) and (5.4) it is clear that the characteristic dynamical response times of $m(t)$ and $y(t)$ are $1/\mu_1$ and $1/\mu_2$, respectively. In many natural settings, the snail lifetime $(1/\mu_2)$ is typically a few weeks or less, while the adult schistosome lifetime $(1/\mu_1)$ is typically in excess of one year. Such circumstances correspond to $\mu_2 \gg \mu_1$. It follows that $y(t)$ has a much faster response time than $m(t)$, and the dynamical trajectories tend to become vertical lines in the y-m plane, parallel to the y-axis. In particular, the dashed "breakpoint" line in Fig. 3 straightens to a *vertical* line through m_B. In this extreme case $\mu_2 \gg \mu_1$, we may effectively take the fraction of snails infected as being instantaneously adjusted to the stationary value specified by the isocline (5.6); the system reduces to a single dynamical equation for the variable $m(t)$,

$$\frac{dm}{dt} = \mu_1 \left[\frac{\frac{1}{2} T_1 T_2 m \phi}{1 + \frac{1}{2} T_2 m \phi} - m \right]. \tag{5.7}$$

The approximation $\mu_2 \gg \mu_1$ is implicit in MacDonald [22] and Lee and Lewis [18]. Both these works deal with the single variable $m(t)$. Indeed, it can be seen that MacDonald's quantities A, B, and α are $A = T_1 \mu_1$, $B = \frac{1}{2} T_2 \mu_2$, and $\alpha = \phi(m, \infty)$, so that Eq. (5.7) is exactly MacDonald's [22, Eq. (15)] equation for $m(t)$. Further, it is clear why MacDonald can speak of *the* breakpoint: in his (implied) limit $\mu_2 \gg \mu_1$, the dashed line in the generic Fig. 3 is vertical, and all initial $m < m_B$ are attracted to the origin, independent of the initial value of y.

There are, however, some situations where the snails are long-lived (e.g., some Brazilian snails live for one year or more), so that μ_2 is not greatly in excess of μ_1. The pair of dynamical equations (5.1) and (5.4) must then be retained, and the "breakpoint" phenomenon is more complicated. As can be seen from Fig. 3, for relatively large values of y one can have initial values of m which are less than m_B but are nevertheless to the right of the dashed line, consequently being attracted to m^*; conversely, for relatively small y, one can have $m(0)$ which exceed m_B but are nevertheless attracted to the origin. These complications in the breakpoint concept are discussed more formally by Nasell ([27, 28]; see also Nasell and Hirsch in [12]—all this work is for $k \to \infty$). But for $\mu_2 \gg \mu_1$, the complications do not arise.

Another interesting study, which also implicitly embodies the assumption $\mu_2 \gg \mu_1$, is due to Rosenfield [30, 31]. Her work differs from MacDonald [22] and its relatives in two ways. The first, and minor, difference is that the dynamical variable is chosen to be the prevalence of pairs Ω (which by assumption is equal to the fraction of the population passing eggs), rather than the mean worm load m. The second, and major, difference is that Rosenfield describes the dynamical behavior of Ω not by a theoretically

derived expression such as the RHS of Eq. (5.7), but rather by a phenomenological formula fitted to data. Rosenfield's equation for $\Omega(t)$ is basically

$$\frac{d\Omega}{dt} = A(1-\Omega) - B\Omega. \tag{5.8}$$

Here B is essentially $2\mu_1$, and A is defined by the empirical formula

$$A = b_0 H^{b_1} P^{b_2}, \tag{5.9}$$

where H is the amount of accessible snail habitat (in meters of water line per village), P is the number of people per village passing eggs (i.e., $P = N_1\Omega$), and b_0, b_1, b_2 are determined by a regression analysis of several years of data from 14 villages in Iran. With these definitions, P is linearly proportional to $T_2\Omega$, and it is reasonable to assume that H is linearly proportional to N_2 and thence to T_1. Furthermore, Ω is typically small in the Iranian studies (see, e.g., [30], Table 5 on p. 84 and Table 6 on p. 87: the maximum Ω is around 40%, with typical values around 10% or less), so that Eq. (5.8) is roughly

$$\frac{d\Omega}{dt} \approx C T_1^{b_1} T_2^{b_2} \Omega^{b_2} - 2\mu_1\Omega. \tag{5.10}$$

Here C is some passive numerical constant. We can now compare this phenomenological equation (5.10) with the corresponding purely theoretical relation derived from Eq. (5.7). For relatively small Ω, Eq. (2.28) for case I or Eq. (3.19) for case II enables us to rewrite Eq. (5.7) as

$$\frac{d\Omega}{dt} \approx C' T_1 \Omega^{1/2} \left[\frac{T_2\psi}{2 + T_2\psi} \right] - 2\mu_1\Omega. \tag{5.11}$$

Here C' is the quantity $\mu_1[(1+k)/k]^{1/2}$ for case I or μ_1 for case II, and ψ is the average number of paired worms, defined by Eq. (2.14). For sufficiently large values of T_2, the factor in square brackets will be effectively unity unless Ω is very small, whereupon Eqs. (5.10) and (5.11) can be directly compared: with $b_1 = 1$ and $b_2 = \frac{1}{2}$ the equations agree in their dependence on T_1 and Ω, and disagree in their dependence on T_2. In fact, Rosenfield's purely empirical values are $b_1 = 1.11$ and $b_2 = 0.46$. This remarkable agreement may be largely coincidental. The discrepancy with respect to the dependence on T_2 could well stem from Rosenfield's procedure of taking regressions on the combined quantity $T_2\Omega$, or, more literally, $N_1\Omega$: as the 57 villages ultimately involved in the study ranged in size only from 60 to 600 people [30, p. 61], whereas values of Ω varied over two full orders of magnitude [30, p. 87], it may plausibly be argued that the index b_2 for the

combination $T_2\Omega$ is dominated by the dependence on Ω, so that Eq. (5.10) describes the Ω-dependence more accurately than the T_2-dependence.

This discussion of the relation between Rosenfield's phenomenological Eq. (5.8) and more abstractly theoretical models has necessarily been very untidy and imprecise. I think such relations need to be explored, no matter how crudely, because this kind of empirical model seems well suited to the reduction of data and the practical design of control measures.

6. THRESHOLD AND BREAKPOINT

As discussed above, the possible equilibrium points for the pair of dynamical equations (5.1) and (5.4) are determined by the intersection of the isoclines (5.5) and (5.6). From Eqs. (5.5) and (5.6), it is clear that one solution is always the origin,

$$m = 0, \tag{6.1}$$

along with $y = 0$. Other equilibrium values of m are given by

$$T_2 (T_1 - m)\phi(m,k) = 2. \tag{6.2}$$

A graphical procedure for solving Eq. (6.2) is as follows. First, construct the function $f_1(m) \equiv 2/\phi(m)$; for given k and assumptions about the distribution of female and male worms, ϕ is given by Eq. (2.15) or (3.10), and it can be seen that $f_1(m)$ as a function of m is always curved inwards toward the origin, with $f_1 \to \infty$ as $m \to 0$ and $f_1 \to 2$ as $m \to \infty$. Second, construct the function $f_2(m) \equiv T_2(T_1 - m)$; this is a straight line with negative slope, and depending on the particular values of T_1 and T_2 it intersects $f_1(m)$ either at two points, or not at all. The dividing or *threshold* condition occurs when $f_2(m)$ is exactly tangential to $f_1(m)$: this gives the threshold relationship among m, T_1, and T_2 to be

$$T_2 = 2\frac{d\phi/dm}{\phi^2}, \tag{6.3}$$

$$T_1 = m + \frac{\phi}{d\phi/dm}. \tag{6.4}$$

Thus, for any given functional form of $\phi(m)$, the threshold relation between T_1 and T_2 may readily be calculated by using the threshold m as an implicit variable in Eqs. (6.3) and (6.4). This whole operation is discussed more fully and rigorously, albeit for the special Poisson case of $\phi(m, \infty)$ of Eq. (2.19), in [25].

Figures 4 and 5 show the results of such calculations. Figure 4 is for case I, where female and male worms are distributed together [ϕ_t given by Eq.

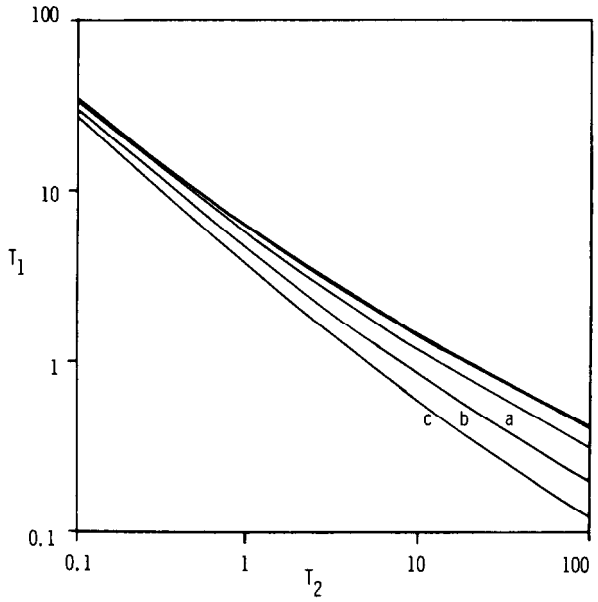

FIG. 4. The threshold criteria for the transmission coefficients T_1 (snail to man) and T_2 (man to snail) are illustrated for various degrees of worm aggregation in case I, both sexes aggregated together. In the parameter region above a given curve, the infection can be maintained; below, the only equilibrium state is at $m=0$. The thick curve is the "reference" case of independently randomly distributed worms (i.e., the Poisson limit, $k\to\infty$). The other curves are for (a) $k=1$, (b) $k=0.2$, (c) $k=0.05$. Note that for case I, the higher the degree of worm aggregation, the lower the threshold.

(2.15)], and Fig. 5 is for case II, where female and male worms are distributed separately [ϕ_s given by Eq. (3.10)]. It is clear that for case I, the infection can be more easily maintained (i.e., maintained for relatively smaller values of the transmission parameters T_1 and T_2) when the worms are more clumped (i.e., for smaller values of k). Conversely, for case II the infection is less easily maintained (i.e., maintenance requires relatively larger values of T_1 and T_2) as the separate distributions of female and of male worms become more clumped (i.e., smaller k). These tendencies, and the inferences and practical recommendations to be drawn from them, are discussed more fully in BM.

Figures 4 and 5 may usefully be supplemented by some analytic relations between T_1 and T_2 for limiting cases.

For case I, the limiting forms (2.32) and (2.29) for $\phi_t(m,k)$ in the limits of large and small m, respectively, may be used in Eqs. (6.3) and (6.4) to arrive,

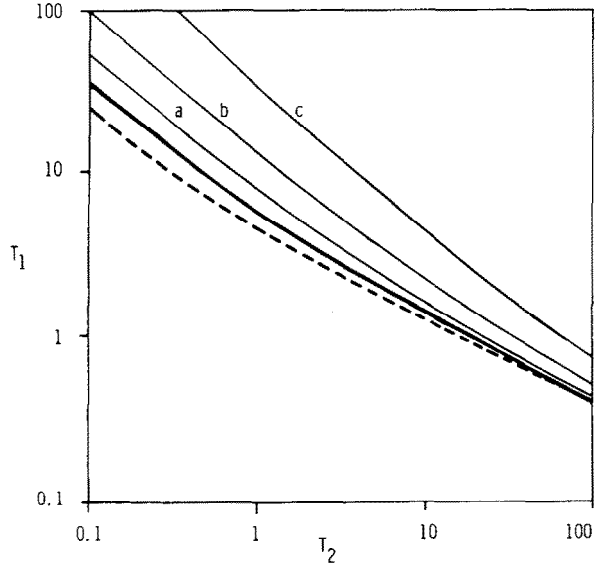

FIG. 5. Same as in Fig. 4, except that here the worm aggregation is according to case II, where the sexes are separately aggregated, each in a negative binomial with clumping parameter k. Again the thick solid curve is for the Poisson limit, $k\to\infty$, and the thin solid curves are for (a) $k=1$, (b) $k=0.2$, (c) $k=0.05$. For case II, the higher the degree of aggregation, the higher the threshold. As in Fig. 4, the worms are assumed to mate monogamously; for comparison, the thick dashed curve shows the threshold relation for a promiscuous mating system, in the Poisson limit of independently randomly distributed worms ($k\to\infty$), as discussed in Appendix C.

after some routine manipulation, at the results

$$T_1T_2=2 \qquad \text{for} \quad T_2\ll\frac{1+k}{4k}, \tag{6.5}$$

$$T_1T_2^{1/2}=4\left(\frac{k}{1+k}\right)^{1/2} \qquad \text{for} \quad T_2\gg\frac{1+k}{4k}. \tag{6.6}$$

The corresponding results for case II can be obtained in a similar way from the formulae (3.23) and (3.20) for $\phi_s(m,k)$ in the limit of large and small m, respectively. These threshold results are

$$T_1T_2=2/\kappa(k) \qquad \text{for} \quad T_2\ll 1/4\kappa^2, \tag{6.7}$$

$$T_1T_2^{1/2}=4 \qquad \text{for} \quad T_2\gg 1/4\kappa^2. \tag{6.8}$$

Here $\kappa(k)$ is as defined by Eq. (3.24). In particular, for case II in the special

case $k=1$, we can use Eq. (3.13) for $\phi_s(m,1)$ to get the fully exact threshold relation

$$T_1 T_2 = 4\left(1+\sqrt{T_2}\right). \tag{6.9}$$

These results shed light on a controversial recommendation urged by MacDonald [22, 23]. His numerical studies (for the Poisson limit $k\to\infty$) led him to conclude that the threshold condition is more sensitive to changes in T_1 (snails to man) than to changes in T_2 (man to snails), and hence that "safe water supplies are more important than latrines". For $k\to\infty$, such a conclusion indeed follows from Eq. (6.6) or (6.8) for "large" T_2 (which was apparently the case in MacDonald's simulations); if the limiting equation (6.6) or (6.8) applies, a 4-fold reduction in T_1 brings one 4 times closer to threshold, whereas a 4-fold reduction in T_2 brings one only 2 times closer. N. G. Hairston (private communication) and others have, however, suggested that this conclusion depends on the numerical details of the parameters. We see that this is indeed so, and that in the limit of Eq. (6.5) or (6.7) for "small" T_2 (see below), the threshold is equally sensitive to T_1 and T_2. These remarks have been made more formally and exactly, although possibly somewhat less transparently, by Nasell ([27, 28]; see also Nasell and Hirsch, [25] and in [12]) for the special case $k\to\infty$.

Two further important observations can be made.

First, in the MNH Poisson limit of independently randomly distributed worms ($k\to\infty$), the distinction between "large T_2" [Eqs. (6.6) and (6.8)] and "small T_2" [Eqs. (6.5) and (6.7)] occurs very roughly around $T_2\sim 1$. For highly clumped distributions ($k\to 0$), either for case I [Eqs. (6.5) and (6.6)] or for case II [Eqs. (6.7) and (6.8)], the limit of "large T_2", to which MacDonald's recommendations apply, requires much bigger values of T_2, roughly in excess of $T_2\sim 1/k$ for case I or, even more severely, in excess of $T_2\sim 1/k^2$ for case II. That is, the range of values of T_1 and T_2 to which MacDonald's remarks apply is significantly diminished if the worms are clumped.

Second, any practical control measures must take account of the economic costs as well as the biological dynamics of transmission. The cost functions associated with changes in T_1 and T_2 may easily contain power-law dependences that more than compensate the "$\sqrt{T_2}$ effect" exhibited by Eqs. (6.6) and (6.8).

The above discussion is all for the case of monogamous worms. As set out in Appendix C, the qualitative conclusions remain intact for a promiscuous mating system. For any given value of k, the infection is of course easier to maintain with promiscuous than with monogamous worms, but the effects are quantitative rather than qualitative. All the general trends are unaltered. Figure 5 shows the threshold relation between T_1 and T_2 for

promiscuous worms in the Poisson limit ($k \to \infty$); some explicit formulae are given in Eqs. (C.13) through (C.17) in Appendix C.

Above threshold, Eq. (6.2) has two solutions, corresponding to the points m^* and m_B discussed in the preceding section (see Fig. 3). For given T_2, and specified $\phi(m,k)$, the stable equilibrium value of m as a function of the transmission parameter T_1 may be obtained directly from Eq. (6.2). For case I, we use $\phi_I(m,k)$ from Eq. (2.15) to display this relation, for some particular values of k, in Fig. 6. For any one value of k, we see that the

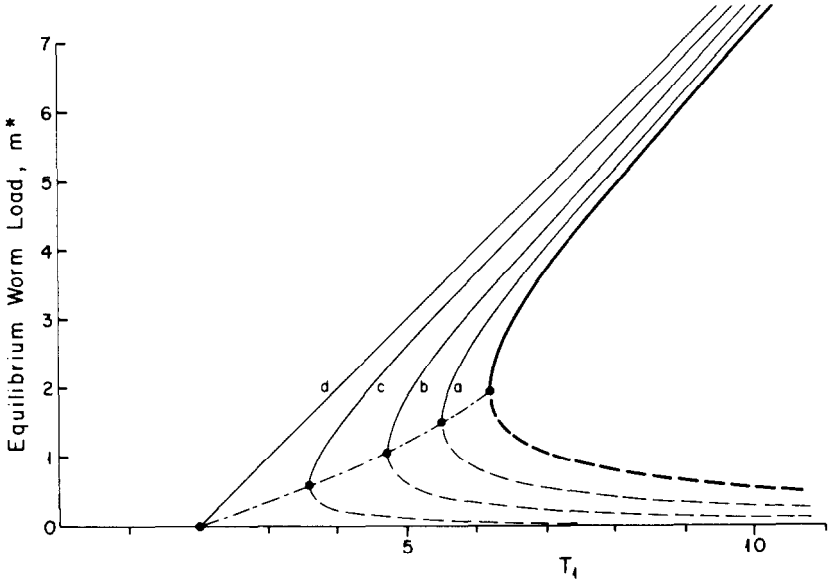

FIG. 6. The equilibrium values of the mean worm load, m^*, are shown as a function of the transmission coefficient T_1 (snail to man), for a particular value of T_2 ($T_2 = 1$), and for various degrees of worm aggregation in case I (sexes distributed together). The thick curve to the right is for the Poisson "reference" case, $k \to \infty$: below the threshold value of T_1, the only equilibrium value is at $m = 0$; at threshold there discontinuously appears a second equilibrium value, m^*, at a finite value of m (denoted by the solid dot); as T_1 increases beyond threshold there continue to be two equilibrium states, one at $m = 0$ and one at an increasing, finite value m^*. The dashed line illustrates the "breakpoint" value, m_B: for $\mu_2 \gg \mu_1$, all $m > m_B$ are attracted to m^*, and all $m < m_B$ to the origin; more generally, the breakpoint phenomenon is more complicated (cf. Fig. 3). The thin solid and dashed curves depict the corresponding situations for (a) $k = 1$, (b) $k = 0.2$, (c) $k = 0.05$, and (d) the limit $k \to 0$. Note that as aggregation increases (as k decreases), the breakpoint phenomenon becomes less conspicuous, finally disappearing in the limit $k \to 0$ (when a "malaria-like" curve, with no discontinuity or breakpoint, is recovered). The dot-dashed line connects the threshold values of m^*, from $k \to 0$ through $k \to \infty$.

infection cannot be maintained for small T_1. At the threshold value of T_1 there appears a second stable state at a finite value of m, and thereafter there are two alternative stable states ($m=0$ and $m=m^*$). Between these two states lies the value m_B, which is *the* "breakpoint" value if $\mu_2 \gg \mu_1$; as explained earlier, and emphasized by Nasell and Hirsch (in [12]), for more general values of μ_2 and μ_1 the dissection of the m-y plane into the domains of attraction of $m=0$ and of $m=m^*$ is more complicated. Notice that as k gets smaller, corresponding to more clumped worm distributions, the threshold is lowered and the breakpoint phenomenon is less conspicuous. A similar figure, with similar features, can be obtained for m as a function of T_2, for given T_1.

For case II [$\phi_s(m,k)$ given by Eq. (3.10)], the figure corresponding to Fig. 6 is given in BM. Here, in contrast with Fig. 6, increased clumping (smaller k) makes for a raised threshold and enhanced breakpoint phenomenon. The intuitive explanations and practical implications of these results, for both cases I and II, are discussed more fully in BM.

One final point concerns the effect of such density-dependent considerations as host immune response, worm death rate depending on worm load, or rate of egg production depending on worm density. Although the details will not be pursued here, the basic effect in each case is to make for relatively low levels of equilibrium worm load m^* at high levels of transmission—i.e., to modify Fig. 6 in such a way that m rises less steeply with T_1 for large T_1. For general discussion of these points, see [3].

7. LATENCY IN SNAIL INFECTIONS

So far we have followed most previous authors in having two kinds of snails: the fraction $(1-y)$ not infected by a miracidium, and the fraction (y) that are both infected and shedding cercariae. One consequence, which follows from Eq. (5.6), is that for $T_2\psi(m)$ significantly in excess of unity (which is usually the case if the equilibrium mean worm load exceeds unity) nearly all snails are shedding cercariae; that is, $y^* \approx 1$. This is, however, grossly discrepant with the observed facts (see, e.g., [12, 34]), which are that even when schistosomiasis is very prevalent the fraction of snails shedding cercariae rarely exceeds 10%, and is typically less than, or of the order of, 1%.

This discrepancy may be explained, at least in part, by noting that a latent period (of duration τ) elapses between the time when a snail becomes infected by a miracidium and the time when it begins to shed cercariae. Such a latent period has been included in a MacDonald-like model (with worm load the only dynamical variable) by Lee and Lewis [18], and Nasell [26] and Lewis [19] have studied the effects of a transition rate (as opposed to a specific latent period) from infected to shedding stages. All these studies have independently randomly distributed adult worms (i.e., the

Poisson limit $k \to \infty$). Nasell gives a formal analytic study, and the other authors give numerical simulations.

In this section, we show how the effects of such a latent period can be incorporated simply yet generally into the study of the transmission dynamics. This is done for arbitrary k. Particular attention is given to the threshold and breakpoint phenomena, and to the equilibrium fraction of snails, y^*, that are shedding.

To begin, we retain the assumption that the total number of snails, N_2, is constant, and define (with some alphabetical awkwardness) x to be the fraction not infected (which have a death rate μ_2), z the fraction infected but not yet shedding (with death rate μ_2'), and y the fraction shedding cercariae (with death rate μ_2''). By definition,

$$x + y + z = 1. \tag{7.1}$$

The fraction z is in balance between a gain term and two loss terms. The gain term, as in Eq. (5.2), is the infection rate per snail, h_2, times the fraction uninfected, x. One loss term comes directly from snail deaths. The other loss comes from snails that make the transition to the shedding fraction y: this term is equal to the fraction of snails that entered the z-class at time $t - \tau$, times the probability ($e^{-\mu_2'\tau}$) that they have not died in the intervening time interval τ. Thus the equation for $z(t)$ is

$$\frac{dz}{dt} = h_2 x(t) - h_2 e^{-\mu_2'\tau} x(t-\tau) - \mu_2' z(t). \tag{7.2}$$

The final fraction y is in balance between gain from the z-class and death:

$$\frac{dy}{dt} = h_2 e^{-\mu_2'\tau} x(t-\tau) - \mu_2'' y(t). \tag{7.3}$$

By using Eq. (7.1) for $x(t)$ and Eq. (5.3) for h_2, we can express Eqs. (7.2) and (7.3) in terms of the three dynamical variables $m(t)$, $y(t)$, and $z(t)$. This, in conjunction with Eq. (5.1) for dm/dt, gives a set of three coupled, first order differential equations for these three variables. It is obvious that such a dynamical investigation is significantly more complicated than the two-variable system of Sec. 5.

For the threshold and breakpoint equations, we require only the equilibrium values of x, y, and z. These are readily obtained from Eqs. (7.1), (7.2), and (7.3) by putting $dy/dt = dz/dt = 0$, and noting that $x(t) = x(t-\tau) = x^*$. After some algebraic manipulation, one gets

$$x^* = \mu_2' \mu_2'' / D, \tag{7.4}$$

$$z^* = h_2 (1 - f) \mu_2'' / D, \tag{7.5}$$

$$y^* = h_2 f \mu_2' / D, \tag{7.6}$$

where

$$D = h_2\left[f\mu_2' + (1-f)\,\mu_2'' \right] + \mu_2'\,\mu_2''. \tag{7.7}$$

Here $h_2 = \frac{1}{2}\mu_2 T_2 m\phi(m,k)$ is as defined by Eq. (5.3), using the death rate for unifected snails. For convenience in notation, f is defined as

$$f = e^{-\mu_2'\tau}, \qquad 1 > f > 0. \tag{7.8}$$

A more explicit expression for the y^* of Eq. (7.6) is therefore

$$y^* = \frac{\frac{1}{2}T_2 m\phi f}{(\mu_2''/\mu_2) + \frac{1}{2}T_2 m\phi\left[f + (1-f)(\mu_2''/\mu_2') \right]}. \tag{7.9}$$

The possible equilibrium values of m are, as before, given by the intersection of the isoclines (5.5) and (7.9), the latter being the generalization of Eq. (5.6). Again $m=0$ is always one solution. Other possible solutions follow from

$$\tilde{T}_2\,[\tilde{T}_1 - m]\phi(m,k) = 2. \tag{7.10}$$

Here the transmission coefficients $\tilde{T}_1$ (snails to man) and $\tilde{T}_2$ (man to snails) have been redefined as

$$\tilde{T}_1(\tau) = \frac{T_1 f}{f + (1-f)(\mu_2''/\mu_2')}, \tag{7.11}$$

$$\tilde{T}_2(\tau) = T_2\left[f + (1-f)\frac{\mu_2''}{\mu_2'} \right]\frac{\mu_2}{\mu_2''}. \tag{7.12}$$

The quantity f is as defined by Eq. (7.8).

This is a very useful result. It means that, for the more realistic case where infected snails have a latent period before they begin shedding, the entire discussion of Sec. 6 remains true, subject to the simple alteration that T_1 and T_2 are to be reinterpreted according to Eqs. (7.11) and (7.12). Note in particular that the effective transmission coefficient $\tilde{T}_1$ (snails to man) is always diminished by the existence of a latent period.

Furthermore, in the limit $T_2 m\phi \gg 1$, the equilibrium fraction of snails observed to be shedding is, from Eq. (7.9),

$$y^* \to \frac{f}{f + (1-f)(\mu_2''/\mu_2')}. \tag{7.13}$$

In the limit $\tau \to 0$ (and thence $f \to 1$), the earlier result $y^* \to 1$ is recovered. More generally, this limiting value of y^* is less than unity, and substantially

TABLE 1

Equilibrium Fraction of Snails That Are Shedding Cercariae, $y^*(m \to \infty)$[a]

Latent period, τ (days)	Mean life of infected-but-latent snails, $1/\mu_2'$ (days)	Mean life of snails shedding cercariae, $1/\mu_2''$ (days)	Equilibrium fraction of shedding snails, y^* (percent)
30	30	30	37
30	30	7	12
30	7	7	1.4

[a]In the limit of very high worm prevalence among the human hosts [see Eq. (7.13)], for various illustrative values of τ, μ_2', μ_2''.

so if f is small. This goes some way toward explaining the observed values of y^* that were mentioned above; some illustrative numerical examples are given in Table 1.

In the special case where the death rate for infected snails is independent of whether the snails are latent or shedding ($\mu_2' = \mu_2''$), the above results simplify. The effective transmission coefficients become

$$\tilde{T}_1(\tau) = T_1 e^{-\mu_2' \tau}, \tag{7.14}$$

$$\tilde{T}_2(\tau) = (\mu_2/\mu_2') T_2. \tag{7.15}$$

That is, the effect is to diminish T_1 by the latency factor $e^{-\mu_2' \tau}$, and to diminish T_2 by the death rate ratio μ_2/μ_2': all the equations in Sec. 6 may be reread in this light. The effect is analogous to MacDonald's celebrated $e^{-\mu\tau}$ or p^n in the malaria threshold relation [9, 21]. The limiting expression (7.13) for the equilibrium fraction of snails shedding cercariae is similarly simple when all infected snails have the same death rate:

$$y^* \to e^{-\mu_2' \tau}. \tag{7.16}$$

These consequences of snail latency are reviewed in conjunction with such observational data as are available for μ_2, μ_2', μ_2'', and τ, and the implications for the overall transmission dynamics are discussed, in another paper (D. J. Bradley and R. M. May, in preparation).

8. CONCLUSION

In conclusion, some of the remaining problems are summarized.

As mentioned in Secs. 5 and 6, the dynamical equations for $m(t)$ and $y(t)$, and the resulting isoclines (as illustrated in Figs. 2 and 3), can be made more complicated by the inclusion of nonlinearities in various rate processes: these include density dependence in the adult-worm death rate, per capita fecundity that depends on the number of egg-producing female worms in the human host, immune response by the host, and (less plausibly) "superinfection" of snails by miracidiae. Most of these effects can be handled, at least qualitatively, by the graphical "phase-plane" techniques of Sec. 6. Replacing the passively constant snail population N_2 by some appropriate description of the snails' single-species population dynamics, $N_2(t)$ (see, e.g., [24], Chapter 2) introduces a realistic complication that is difficult to handle except by numerical simulations.

However, the most substantial complications are undoubtedly those that stem from the spatial and sociological aspects of the transmission dynamics. Significant components of the cycle (e.g., the rate at which snails are exposed to miracidiae, derived from the rate at which humans excrete eggs into snail habitats; or the rate of human exposure to cercariae) depend a lot

on the age and sex of the humans in question. These contact rates depend also on the local geography of the water supplies, and on social patterns of their usage (see, e.g., [35]).

These problems are possibly less severe with some filarial infections, which (like malaria) pass back and forth in direct contact between man and various specific kinds of flies, without the intervening complication of stages where the parasite exists by itself (as cercaria or miracidium), seeking its host in the water. Even here, however, the data typically testify to age and sex dependence in the patterns of infection.

One possible line of attack (which differs from the phenomenological approach of this paper) is to use some very simple model for these spatial and/or sociological patterns of transmission, in order to derive the distribution function for adult worms among their human hosts (e.g., Anderson [2]; K. Dietz, private communication).

Finally, before drawing public-health lessons even from relatively realistic models, the economic costs of control strategies need to be woven in. Conclusions drawn from purely biological models for systems with consequential economic and political components can be misleading, and sometimes distressingly so (see, e.g., [6]).

This paper has been restricted largely to the mathematical presentation of various things that may complicate the transmission dynamics of schistosomiasis and other similar helminthic infections: worm aggregation in the primary host; its effects on threshold and breakpoint phenomena; latent periods for infected snails; promiscuous mating among worms. The mathematical results having been established here, their implications for data analysis and for practical control measures are developed elsewhere (in the literature aimed at public-health people).

APPENDIX A

In this appendix, we derive the general expression (2.15) for the mating probability ϕ_t for monogamous worms when both sexes are distributed together (distributed among hosts as a negative binomial with mean m and parameter k). The limiting formulae given in the main text are also derived.

This calculation is best done by first noting that for an even number of worms, $i = 2j$, each of which is either female or male (each with probability $\frac{1}{2}$), the average *fraction* of worms that are *not* sexually paired is

$$\frac{(2j)!2^{-2j}}{j!j!}. \tag{A.1}$$

This same formula applies if the total number of worms is odd, $i = 2j + 1$; that is, the average fraction not paired among an odd number of worms is

the same as for the preceding even number. The result (A.1) has been given by MacDonald [22] (but note the misprints) and by Nasell [28].

The total number of paired worms in case I is then

$$\psi_t(m,k) = m - \sum_{i=0}^{\infty} iP(i|m,k)(\text{fraction } \textit{not} \text{ paired}). \tag{A.2}$$

Here $P(i|m,k)$ is the probability to have i worms, regardless of sex, as given by Eq. (1.1); the fraction not paired is given by Eq. (A.1). Then, using Eq. (2.14),

$$m\phi_t(m,k) = m - \sum_{j=0}^{\infty} \left[2jP(2j|m,k) + (2j+1)P(2j+1|m,k) \right] \frac{2^{-2j}(2j)!}{(j!j!)}. \tag{A.3}$$

Substituting from Eq. (1.1), we have

$$\phi_t(m,k) = 1 - \frac{(1-\alpha)^k}{m\Gamma(k)} \sum_{j=0}^{\infty} \frac{(\alpha/2)^{2j}}{j!j!} \left[(2j)\Gamma(2j+k) + \alpha\Gamma(2j+1+k) \right]. \tag{A.4}$$

Using the definition

$$\Gamma(z) = \int_0^{\infty} x^{z-1} e^{-x}\, dx, \tag{A.5}$$

Eq. (A.4) can be written

$$\phi_t(m,k) = 1 - \frac{(1-\alpha)^k}{m\Gamma(k)} \int_0^{\infty} e^{-x} x^{k-1}\, dx \sum_{j=0}^{\infty} \frac{(\alpha x/2)^{2j}}{j!j!} (2j + \alpha x). \tag{A.6}$$

But the summations can now be rewritten using (see AS, formulae 9-6-10, 9-6-6, 9-6-16, and 9-6-19)

$$\sum_{j=0}^{\infty} \frac{(\alpha x/2)^{2j}}{j!j!} = I_0(\alpha x) = \frac{1}{2\pi} \int_0^{2\pi} e^{-\alpha x \cos\theta}\, d\theta, \tag{A.7}$$

$$\sum_{j=0}^{\infty} \frac{2j(\alpha x/2)^{2j}}{j!j!} = \alpha x I_1(\alpha x) = \frac{-\alpha x}{2\pi} \int_0^{2\pi} e^{-\alpha x \cos\theta} \cos\theta\, d\theta. \tag{A.8}$$

This gives

$$\phi_t(m,k) = 1 - \frac{\alpha(1-\alpha)^k}{2\pi m\Gamma(k)} \int_0^{2\pi} (1-\cos\theta)\, d\theta \int_0^{\infty} x^k e^{-x(1+\alpha\cos\theta)}\, dx. \quad \text{(A.9)}$$

Or, performing the integral over x, and using the equation (1.2) which relates α, m, and k [whence $\alpha k = m(1-\alpha)$],

$$\phi_t(m,k) = 1 - \frac{(1-\alpha)^{1+k}}{2\pi} \int_0^{2\pi} \frac{(1-\cos\theta)\, d\theta}{(1+\alpha\cos\theta)^{1+k}}. \quad \text{(A.10)}$$

Equation (A.10) is, in my view, the most useful form for $\phi_t(m,k)$. An equivalent expression in terms of the hypergeometic function (AS, Chapter 15) can be obtained by working directly from the sums in the expression (A.4) above:

$$\phi_t(m,k) = 1 - (1-\alpha)^{1+k}\left[1 + \left(\frac{1+\alpha}{\alpha}\right)\frac{d}{d\alpha}\right] F\left(\tfrac{1}{2}k, \tfrac{1}{2}k + \tfrac{1}{2}|1|\alpha^2\right). \quad \text{(A.11)}$$

Or, as a further variant, the definition of the generalized Legendre function,

$$P_k^0(z) \equiv \frac{1}{2\pi} \int_0^{2\pi} \frac{d\theta}{\left(z + \sqrt{z^2-1}\,\cos\theta\right)^{1+k}}, \quad \text{(A.12)}$$

[16, p. 25] can be used in Eq. (A.10) to express $\phi_t(m,k)$ in terms of this function and its first derivative: such a formula has been obtained by K. Dietz (private communication).

In *the limit* $k \to \infty$ (and therefore $\alpha \to m/k \to 0$), Eq. (2.16) may be used to write

$$\phi_t(m,\infty) \to 1 - \frac{e^{-m}}{2\pi} \int_0^{2\pi} (1-\cos\theta) e^{-m\cos\theta}\, d\theta. \quad \text{(A.13)}$$

Using the definitions of $I_0(m)$ and $I_1(m)$ set out in Eqs. (A.7) and (A.8), this gives the well-known limiting result (2.19).

In the opposite *limit* $k \to 0$, we may neglect terms of relative order k by putting the exponents $1+k \to 1$ in Eq. (A.10). Unless m is less than or of the order of k, we also have α approaching unity; but as this introduces a singularity into the integrand in Eq. (A.10), this aspect of the limit needs to be treated circumspectly. Retaining the exact expression for α, but other-

wise neglecting terms of relative order k, we have

$$\phi_t(m,k\to 0)=1-\frac{1-\alpha}{2\pi}\int_0^{2\pi}\frac{(1-\cos\theta)\,d\theta}{1+\alpha\cos\theta}. \tag{A.14}$$

This is a routine integral. It can be evaluated by transforming to the complex variable $z=e^{i\theta}$, and taking the contour integral around the unit circle:

$$\phi_t(m,k\to 0)=1-\frac{1-\alpha}{2\pi i}\oint\frac{(z^2-2z+1)\,dz}{\alpha z^2+2z+\alpha}. \tag{A.15}$$

Standard contour-integral techniques (see, e.g., [5]) then lead to the result (2.25) given in the main text. Similar contour-integral methods can conveniently be used to evaluate the expression (A.10) for $\phi_t(m,t)$ for any integer value of k: the result for $k=1$ is given as Eq. (2.22).

In the *limit* $m\gg k$, we have $\alpha\to 1$, and the integral in Eq. (A.10) is dominated by the contribution from the neighborhood of $\theta=\pi$ (where the denominator is approximately $(1-\alpha)^{1+k}$ with $\alpha\approx 1$). We begin by using Eq. (1.2) to manipulate Eq. (A.10) into the equivalent form

$$\phi_t(m,k)=1-\frac{(k/m)^{1+k}}{2\pi}\int_0^{2\pi}\frac{(1-\cos\theta)\,d\theta}{\left[1+(k/m)+\cos\theta\right]^{1+k}}. \tag{A.16}$$

We now change to the variable ε defined by $\theta=\pi+\varepsilon$, and expand $\cos\theta$ around its value in the neighborhood of $\varepsilon\approx 0$, to get for $m\gg k$ the approximation

$$\phi_t(m,k)=1-\frac{(k/m)^{1+k}}{2\pi}\int_{-\pi}^{\pi}\frac{2\,d\varepsilon\left[1+O(\varepsilon^2)\right]}{\left[(k/m)+\frac{1}{2}\varepsilon^2\right]^{1+k}}. \tag{A.17}$$

Or, defining $t=(m/2k)^{1/2}\varepsilon$,

$$\phi_t(m,k)=1-\frac{(2k/m)^{1/2}}{\pi}\int_{-R}^{R}\frac{dt}{(1+t^2)^{1+k}}. \tag{A.18}$$

Here $R\equiv(m/2k)^{1/2}\pi$, whence $R\gg 1$ for $m\gg k$. The approximation (A.18) neglects terms of relative order k/m; it is to be emphasized that it is an asymptotic series approximation, and not a simple power-series one (see,

e.g., [11]). The integral in Eq. (A.18) is now approximated by

$$2\int_0^\infty \frac{dt}{(1+t^2)^{1+k}} = B\left(\tfrac{1}{2}, k+\tfrac{1}{2}\right) = \frac{\pi^{1/2}\Gamma\left(k+\frac{1}{2}\right)}{\Gamma(k+1)} \tag{A.19}$$

(see AS, 6-2-1). Thus we arrive at the asymptotic approximation, Eq. (2.32), with $c(k)$ defined by Eq. (2.33).

APPENDIX B

In this appendix, we derive formulae for the mating probability, ϕ_s, for monogamous worms when females and males are distributed separately, each according to their own negative binomial distribution with mean $m/2$ and parameter k. The formulae are derived from the general expression (3.10) for the particular cases $k=1$, $k\to 0$, and for $m \gg k$.

For $k=1$, we reorder the double summation in Eq. (3.10) to get

$$\psi_s(m,1) = 2(1-\alpha')^2 \sum_{j=0}^{\infty} j(\alpha')^j \sum_{i=j}^{\infty} \theta_{ij}(\alpha')^i. \tag{B.1}$$

Performing the sum over the geometric series with index i, we have

$$\psi_s(m,1) = 2\left[1-(\alpha')^2\right] \sum_{j=0}^{\infty} j(\alpha')^{2j}. \tag{B.2}$$

The sum here is easily done, to give

$$\psi_s(m,1) = \frac{2(\alpha')^2}{1-(\alpha')^2}. \tag{B.3}$$

Substituting from Eq. (3.3), which relates α' to m and k (where here $k=1$), we obtain Eq. (3.13) for $\phi_s(m,1)$. In a similar (if more tedious) fashion, explicit expressions for $\phi_s(m,k)$ can be obtained for other integer values of k.

For the limit $k\to 0$, we work directly from Eq. (3.10). After first noting that the terms with $i=0$ and $j=0$ make zero contribution, and that $k\Gamma(k) = \Gamma(k+1)$, we neglect terms of *relative* order k to get

$$\psi_s(m, k\to 0) = 2k^2 \sum_{i=1}^{\infty} \frac{(\alpha')^i}{i} \sum_{j=1}^{i} \theta_{ij}(\alpha')^j \left[1+O(k)\right]. \tag{B.4}$$

Again, the sum over j is for a straightforward geometric series and gives

$$\psi_s(m,k\to 0)=\frac{2k^2}{1-\alpha'}\sum_{i=1}^{\infty}\frac{(\alpha')^i}{i}\left[2\alpha'-(1+\alpha')(\alpha')^i\right]\left[1+O(k)\right]. \quad \text{(B.5)}$$

The remaining sum is simply related to the power series expansion for $\ln(1-x)$, whence

$$\psi_s(m,k\to 0)=\frac{2k^2}{1-\alpha'}\left[(1-\alpha')\ln(1-\alpha')+(1+\alpha')\ln(1+\alpha')\right]\left[1+O(k)\right]. \quad \text{(B.6)}$$

Use of Eqs. (2.14) and (3.3) immediately leads to Eq. (3.16) for $\phi_s(m,k\to 0)$.

For $m\gg k$, we have $\alpha'\to 1$, and Eq. (3.10) is dominated by the sum over very many higher-order terms. It is convenient to define ε by

$$\varepsilon\equiv -\ln\alpha'\approx\frac{2k}{m}\left[1+O(k/m)\right]. \quad \text{(B.7)}$$

It follows that $1-\alpha'\approx\varepsilon$. In Eq. (3.10) we now replace sums by integrals to get

$$\psi_s(m,k)=\frac{4\varepsilon^{2k}}{\Gamma(k)\Gamma(k)}\int_0^{\infty} i^{k-1}e^{-\varepsilon i}\,di\int_0^{i} j^k e^{-\varepsilon j}\,dj\left[1+O(k/m)\right]. \quad \text{(B.8)}$$

In obtaining Eq. (B.8), we have used

$$\frac{\Gamma(i+k)}{i!}=i^{k-1}\left[1+O(k/i)\right], \quad \text{(B.9)}$$

together with the crucial observation that in the limit $m\gg k$ the integrals are dominated by the regions where $i,j\sim k/\varepsilon\approx m$ (so that terms of relative order k/i are in effect of relative order k/m, which is by assumption small). Defining new variables of integration by $x=\varepsilon i$ and $y=\varepsilon j$, and also using Eq. (B.7) for ε and Eq. (2.14) for ϕ_s, we arrive at

$$\phi_s(m,k)=\frac{2}{\Gamma(k)\Gamma(k+1)}\int_0^{\infty} x^{k-1}e^{-x}\,dx\int_0^{x} y^k e^{-y}\,dy\left[1+O(k/m)\right]. \quad \text{(B.10)}$$

This establishes the result (3.23), namely that for $m\gg k$ the mating probability $\phi_s(m,k)$ asymptotically approaches a numerical constant $\kappa(k)$, which depends only on k. The explicit formula (3.24) for $\kappa(k)$ of course follows directly from the double integral in Eq. (B.10): I will supply details of the derivation on request.

APPENDIX C. COMPLETELY PROMISCUOUS MATING

The discussion of worm aggregation and its effects on the transmission dynamics of schistosomiasis and other helminthic infections has, throughout the main part of this paper and of BM, been under the usual assumption that the worms have a monogamous mating system. The theoretical literature contains some formal discussion of more general mating systems (e.g., [20]), and the need for further studies has been noted (e.g., [12]).

This appendix presents results for the opposite extreme of a completely promiscuous mating system. This promiscuity is defined to be such that, in a given host, *all* females are mated even if only one male is present. The corresponding mating probability under extreme promiscuity, $\Phi(m,k)$, is then calculated as the probability that a given female will have one or more males cohabiting her host.

The general formulae, along with some limiting cases, are presented first for case I (females and males distributed together) and then for case II (females and males distributed separately).

Case I: *together*. With the sex ratio assumed to be unity, the average number of females per host is $\frac{1}{2}m$. Of this overall average, the number of females who find themselves in a host where all worms are female is given by

$$\sum_{i=0}^{\infty} iP(i|m,k)2^{-i}. \tag{C.1}$$

Here $P(i)$ is the probability of having i worms [given by Eq. (1.1)], and 2^{-i} specifies the probability that all i worms are female. In all other hosts, at least one male is present, and consequently all females are mated. Therefore $\Phi_t(m,k)$, the probability that a given female is mated in this completely promiscuous system, is

$$\Phi_t(m,k) = 1 - \frac{2}{m}\sum_{i=0}^{\infty} iP(i|m,k)2^{-i}. \tag{C.2}$$

The sum may be evaluated with the help of the generating function (1.3):

$$\Phi_t(m,k) = 1 - (1-\alpha)^{1+k}(1-\alpha/2)^{-1-k}. \tag{C.3}$$

That is,

$$\Phi_t(m,k) = 1 - (1+m/2k)^{-1-k}. \tag{C.4}$$

In the limit $k \to \infty$, this becomes

$$\Phi_t(m,\infty) = 1 - e^{-m/2}. \tag{C.5}$$

This result (which could easily have been obtained from first principles) corresponds to the limit of completely independently distributed worms. Notice that, for large m, the promiscuous mating probability Φ converges toward unity significantly faster than the monogamous one, ϕ: the correction terms in Φ diminish as $e^{-m/2}$, as compared with $m^{-1/2}$ for ϕ.

For $k=1$, Eq. (C.4) becomes

$$\Phi_t(m,1)=m(m+4)/(m+2)^2. \tag{C.6}$$

In the limit $k\to 0$, terms of order k^2 may be neglected to get

$$\Phi_t(m,k\to 0)=m/(m+2k). \tag{C.7}$$

Limiting expressions for small and for large m follow readily from Eq. (C.4).

Figure 7 illustrates the promiscuous mating probability Φ_t as a function of m for various values of k. The results are to be compared with Fig. 1.

Case II: *separate*. In this case female and male worms are distributed separately, and therefore the probability that a given female will have at least one male also present in her host is given trivially as

$$\Phi_s(m,k)=1-P(0|m/2,k). \tag{C.8}$$

Here $P(0)$ is the probability for the zero class in a negative binomial with mean $m/2$ and parameter k. Substituting from Eq. (1.1),

$$\Phi_s(m,k)=1-(1+m/2k)^{-k}. \tag{C.9}$$

The limit $k\to\infty$ is, of course, again Eq. (C.5). For $k=1$, we have

$$\Phi_s(m,1)=m/(2+m), \tag{C.10}$$

and for $k\to 0$ Eq. (C.9) gives

$$\Phi_s(m,k\to 0)\approx k\ln\left(1+\frac{m}{2k}\right). \tag{C.11}$$

For $m\gg k$, we have the limiting result

$$\Phi_s(m,k)=1-(2k/m)^k+\cdots. \tag{C.12}$$

That is, the promiscuous mating probability saturates to unity for large m, even for case II: this is in contrast with the behavior manifested by ϕ_s [see Eq. (3.23)].

Again, Fig. 7 illustrates the behavior of Φ_s as a function of m for various k. The contrast between "together" and "separate" within Fig. 7, and the overall similarities between Fig. 7 and Fig. 1, both deserve attention.

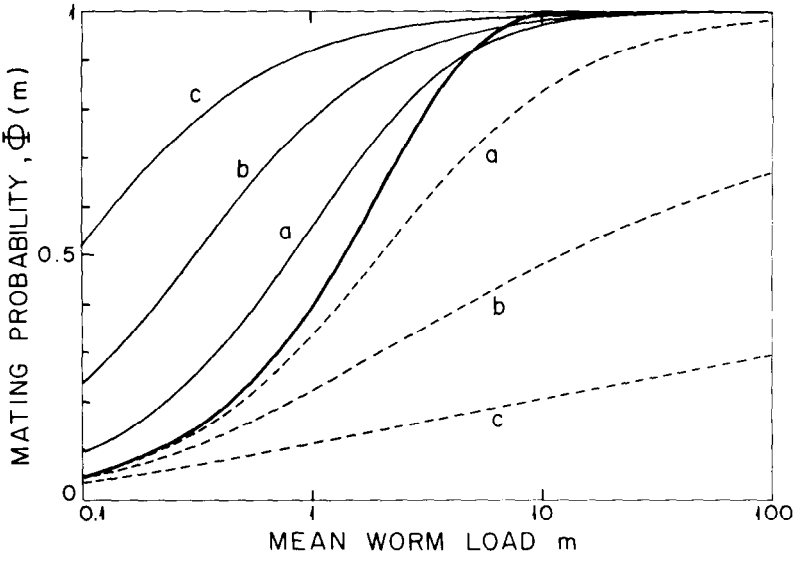

FIG. 7. Probability Φ (cf. Fig. 1) that a given female worm will be mated, as a function of m, for a completely promiscuous mating system. As in Fig. 1, the thick solid curve is for the "reference" Poisson limit, $k \to \infty$. The thin solid curves are for case I (sexes together), and the broken curves are for case II (sexes separate): in either case, (a) is for $k = 1$, (b) for $k = 0.2$, and (c) for $k = 0.05$.

Such evidence as bears on whether schistosomes have a monogamous or a promiscuous mating system is reviewed in BM. The comparison between Figs. 1 and 7 shows that the main features of the dependence of mating probability upon the degree (i.e., k) and kind (i.e., case I or II) of worm clumping are similar for these opposite extremes of monogamous and promiscuous mating systems. This is heartening, for it suggests that the qualitative conclusions about the transmission dynamics of schistosomiasis that emerge from our study (conducted under the assumption of monogamous worms) are robust, and are not sensitively dependent on the details of the mating system.

In either case I or case II, for a given value of k the mating probability is quantitatively higher for promiscuous than for monogamous worms: hence the sexual aspects of the dynamics are less prominent, the "threshold" is somewhat lower, and the dynamics are more "malaria-like".

This may be seen explicitly by using the limiting forms of $\Phi_f(m,k)$ and $\Phi_s(m,k)$, for large and small m, in the threshold equations (6.3) and (6.4). For case I, the promiscuous-worm analogues of the limiting formulae (6.5) and (6.6) are in fact the same as for monogamous worms. For case II, the

promiscuous-worm analogues of Eqs. (6.7) and (6.8) are simpler:

$$T_1 T_2 = 2 \qquad \text{for} \quad T_2 \ll \tfrac{1}{4}, \tag{C.13}$$

$$T_1 T_2^{1/2} = 4 \qquad \text{for} \quad T_2 \gg \tfrac{1}{4}. \tag{C.14}$$

A fully exact formula for the threshold relation between T_1 and T_2 can be given for the special case $k \to \infty$ (independently randomly distributed worms). In this event, we can use Eq. (C.5) in Eqs. (6.3) and (6.4) to get

$$T_1 T_2 = R + 2T_2 \ln\left[1 + \frac{R}{2T_2}\right], \tag{C.15}$$

where

$$R \equiv 1 + (1 + 4T_2)^{1/2}. \tag{C.16}$$

This is illustrated in Fig. 6, which compares the threshold relationship between T_1 and T_2 in the Poisson limit ($k \to \infty$) for promiscuous and for monogamous worms. Another simple, exact result can be obtained for $k = 1$ in case II, where substitution of Eq. (C.10) for $\Phi_s(m, 1)$ into Eqs. (6.3) and (6.4) leads to the threshold relationship

$$T_1 T_2 = 2 + 4T_2^{1/2}. \tag{C.17}$$

This is to be compared with the corresponding exact result (6.9) for monogamous worms.

These explicit comparisons of exact results confirm the point emphasized above, namely that the details of the mating system (as shown by the comparison between the opposite extremes of monogamy and complete promiscuity) have a quantitative rather than a qualitative effect on threshold relations and the like.

The formulae for the prevalence of worms (W) and of pairs (Ω) do not depend on the assumptions made about the mating system.

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REFERENCES

1 M. Abramowitz and I. A. Stegun, *Handbook of Mathematical Functions*, U.S. Natl. Bur. of Stand., Washington, 1964; Dover, New York, 1965.

2 R. M. Anderson, Some simple models of the population dynamics of eucaryotic parasites, in *Mathematical Models in Medicine* (J. Berger et al., Eds.), Lecture Notes in Biomathematics, Vol. 11, Springer, New York, 1976, pp. 16–57.

3 R. M. Anderson and R. M. May, Regulation and stability of host-parasite population interactions, to be published.
4 D. J. Bradley and R. M. May, Consequences of helminth aggregation for the dynamics of schistosomiasis, *Proc. R. Soc. Trop. Med. Hyg.*, to be published.
5 G. F. Carrier, M. Krook, and C. E. Pearson, *Functions of a Complex Variable: Theory and Technique*, McGraw-Hill, New York, 1966.
6 C. W. Clark, *Mathematical Bioeconomics*, Wiley, New York, 1976.
7 J. E. Cohen, Schistosomiasis, a human host-parasite system, in [24], Chapter 13.
8 J. E. Cohen, Mathematical models of schistosomiasis, *Ann. Rev. Ecol. Syst.*, to be published.
9 G. R. Conway, Man versus pests, in [24], Chapter 14.
10 K. Dietz, A pairing process, *Theor. Popul. Biol.* **8**, 81–86 (1975).
11 A. Erdélyi, *Asymptotic Expansions*, Dover, New York, 1956.
12 P. E. M. Fine (rapporteur), *Mathematical Models of Schistosomiasis*, Proc. Workshop Bellagio, Italy, 9–14 May 1976, Edna McConnel Clark Found., New York, 1976.
13 R. A. Fisher, A. S. Corbet, and C. B. Williams, The relation between the number of species and the number of individuals in a random sample of an animal population, *J. Anim. Ecol.* **12**, 42–58 (1943).
14 C. J. Gliddon and D. J. Bradley, Distribution of schistosome pairs in their primary hosts, in preparation.
15 N. G. Hairston, An analysis of age-prevalence data by catalytic models, *Bull. WHO* **33**, 163–175 (1965).
16 E. W. Hobson, *The Theory of Spherical and Ellipsoidal Harmonics*, Cambridge U. P., Cambridge, 1931; Chelsea, New York, 1955.
17 I. G. Kagan, Serologic diagnosis of schistosomiasis, *Bull. N. Y. Acad. Med.* **44**, 262–277 (1968).
18 K. L. Lee and E. R. Lewis, Delay time models of population dynamics with application to schistosomiasis control, *IEEE Trans. Biomed. Eng.* **BME-23**, 225–233 (1976).
19 T. Lewis, A model for the parasitic disease bilharziasis, *Adv. Appl. Probab.* **7**, 673–704 (1975).
20 M. K. Leyton, Stochastic models in populations of helminthic parasites in the definitive host: II, sexual mating functions, *Math. Biosci.* **3**, 413–419 (1968).
21 G. MacDonald, The analysis of equilibrium in malaria, *Trop. Dis. Bull.* **49**, 813–828 (1952).
22 G. MacDonald, The dynamics of helminth infections, with special reference to schistosomes, *Trans. R. Soc. Trop. Med. Hyg.* **59**, 489–506 (1965).
23 G. MacDonald, On the scientific basis of tropical hygiene, *Trans. R. Soc. Trop. Med. Hyg.* **59**, 611–620 (1965).
24 R. M. May, *Theoretical Ecology: Principles and Applications*, Saunders, Oxford; Blackwell, Philadelphia, 1976.
25 I. Nasell and W. M. Hirsch, The transmission dynamics of schistosomiasis, *Commun. Pure Appl. Math.* **26**, 395–453 (1973).
26 I. Nasell, A hybrid model of schistosomiasis with snail latency, *Theor. Popul. Biol.* **10**, 47–69 (1976).
27 I. Nasell, On eradication of schistosomiasis, *Theor. Popul. Biol.* **10**, 133–144 (1976).
28 I. Nasell, On transmission and control of schistosomiasis, with comments on MacDonald's model, to be published.

29 E. C. Pielou, *An Introduction to Mathematical Ecology*, Wiley-Interscience, New York, 1969.
30 P. Rosenfield, *Development and Verification of a Schistosomiasis Transmission Model*, Ph.D. Dissertation, Johns Hopkins Univ., Baltimore, 1975.
31 P. L. Rosenfield, R. A. Smith, and M. G. Wolman, Development and verification of a schistosomiasis transmission model, in preparation.
32 R. F. Sturrock, Field studies on the transmission of *Schistosoma mansoni* and on the bionomics of its intermediate host, *Biomphalaria glabrata*, *Int. J. Parasitol.* **3**, 175–194 (1973).
33 G. M. Tallis and M. K. Leyton, Stochastic models of populations of helminthic parasites in the definitive host: I, *Math. Biosci.* **4**, 39–48 (1969).
34 K. S. Warren, Regulation of the prevalence and intensity of schistosomiasis in man: immunology or ecology? *J. Infect. Dis.* **127**, 595–609 (1973).
35 G. F. White, D. J. Bradley, and A. U. White, *Drawers of Water: Domestic Water Use in East Africa*, Univ. Chic. Press, Chicago, 1972.
36 C. B. Williams, *Patterns in the Balance of Nature*, Academic, London, 1964.