Macdonald's model and the transmission of bilharzia

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Summary

The paper considers a model for the transmission of bilharzia based on Macdonald's assumptions, in the light of data observed in the field. It is shown, in particular, that the threshold parameter governing whether or not an endemic cycle can be established is closely related to the proportion of infected snails in a community, and that this proportion is normally observed to be rather smaller than is compatible with the model. By considering more sophisticated models, allowing for the latent period of infection in the snails, and also for spatial and seasonal heterogeneity, the effective proportion of infected snails, from the point of view of Macdonald's model, is shown to be rather larger, and expressions are given whereby it can be evaluated from observable quantities. However, for the data from Malirong which are taken as illustration, it is also demonstrated that an even more plausible threshold value is obtained from a simple model incorporating human immunity in addition to the assumptions of Macdonald's model, and that, if this model were reasonable, human immunity would appear to be the most important factor in controlling the level of the disease in Malirong.

1. Introduction

In order to arrive at policies for controlling bilharzia, it is useful to have a model of the transmission cycle, from which the qualitative effects of various control measures can be assessed. The first model proposed was that of MACDONALD (1965), and it has since been developed, at the expense of much greater complexity, to incorporate various elements of realism which were ignored in the original formulation: see, for example, NASELL & HIRSCH (1973) and LEWIS (1975). A simplified version of Macdonald's model is also the starting point in this paper, but the developments from it are made in a slightly different spirit. Realistic complication is only introduced in so far as the simple model fails to give satisfactory results, and the aim of the paper is to show to what extent the simple model can be a useful tool for deciding control policies, and to suggest modifications when it breaks down.

In the basic model, transmission is assumed to take place in an isolated homogeneous community. There is a constant total snail population of N: deaths occur among infected snails at a rate δ per infected snail, and each death is compensated by the birth of an uninfected snail. Each infected snail, regardless of how many miracidial penetrations it has suffered, produces cercariae at a rate which results in the development of mature female schistosomes in the human host population at a rate α. Female schistosomes in the human host population have a death rate γ, and each one produces eggs at a rate which gives rise to successful miracidial penetrations of snails at a rate β. α and β are here used as transmission terms which are simple representations of complex sequences of biological processes.

If all the rates are interpreted as differential rates, these assumptions lead to a pair of differential equations for the number X(t) of female schistosomes in the human host population and the number Y(t) of infected snails;

$$\begin{aligned} dX/dt &= -\gamma X + \alpha Y; \\ dY/dt &= -\delta Y + \beta X(1 - Y/N). \end{aligned} \tag{1.1}$$

The factor $(1 - Y/N)$ in the rate of increase of Y(t) reflects the fact that a miracidial penetration only results in an extra infected snail if the snail penetrated was previously uninfected, which will, on the simplest indifference assumption, be the

Table 1—Accessible water area, snail density and proportion of infected snails, for ten colonies in Malirong

Colony	Accessible water area	Snail density	Percentage of infected snails May-June 1954	Percentage of infected snails February-March 1956
Agoong south	5	7·0	0·9	10·8
Malirong pocket no 2	13	6·7	3·6	39·0
Naliwatan upstream	5	10·5	4·8	3·7
Juber creek	3	4·0	4·7	18·7
Nalicaban creek	7	3·5	1·0	8·1
Agoong north	5	6·5	0·0	3·4
Malirong swamp	5	4·5	1·5	5·9
Villaco creek	12	4·6	0·3	13·0
Naliwatan downstream	6	6·3	0·3	2·4
Vicob-Malaigang	8	7·3	0·4	3·7

case a proportion $(1 - Y/N)$ of the time. It is rather more plausible to think of $x(t) \equiv X(t)/N$ and $y(t) \equiv Y(t)/N$ as almost continuous variables, and to write equation (1.1) equivalently as

$$(1.2) \qquad \dot{x} = -\gamma x + \alpha y; \qquad \dot{y} = -\delta y + \beta x(1 - y).$$

The approximation can be expected to hold only in an endemic situation, when individual changes in X and Y are of small importance, and this is the case considered in this paper: the complementary situation is discussed in BARBOUR (1977).

The assumptions made in the model are obviously unrealistic (perhaps one of the most important of the simplifying assumptions is that the total snail population remains constant and transmission is not realistically related to snail or human density) and for instance, they imply that uneven distribution of schistosomes among the human hosts and differing social patterns between groups of human hosts have no effect on transmission. This does not preclude the possibility that the model may be qualitatively reliable, and hence of practical importance. The essential feature of it is the way in which the reproductive cycle of the schistosomes is controlled by the proportion of infected snails, a high proportion infected resulting in a smaller proportion of miracidia causing new snail infections. Without it, the worm population would, on the remaining assumptions of the model, either increase indefinitely, or die out. As it is, equations (1.2) have equilibrium points, found by solving

$$(1.3) \qquad -\gamma x + \alpha y = 0; \qquad -\delta y + \beta x(1 - y) = 0;$$

if $\eta \equiv \alpha\beta/\gamma\delta \leqslant 1$, all trajectories $(x(t), y(t))$ governed by (1.2) converge to (0, 0) as $t \to \infty$, and no endemic situation is possible, whereas if $\eta > 1$, all trajectories coverage to

$$\left(\frac{\alpha}{\gamma} - \frac{\delta}{\beta},\ 1 - \frac{1}{\eta}\right),$$

except when $x(0) = y(0) = 0$. The key threshold parameter η, which governs whether or not an endemic state is possible, and which is a primary target for control measures, depends symmetrically on α, β, γ and δ, though the contact parameters α and β themselves implicitly depend on features such as snail and human population densities, social habits and the like. The current value of η in an endemic situation can, according to the model, be determined by observing the proportion of infected snails, which is predicted to be $1 - 1/\eta$. Typical proportions observed are of the order of 5%, giving η a value around 1·05. This is highly implausible in view of the obviously stable transmission cycle, since a change of 10% in highly variable factors such as α and β would apparently be enough to cut transmission. It is with this aspect of the model that the paper is principally concerned.

2. The latent period of infection in snails

There is a straightforward way in which the proportion of infected snails may be consistently underestimated. In the basic model, a snail is infected as soon as it is successfully penetrated by a miracidium. In practice, snails are diagnosed as infected either when they can be observed to shed cercariae or when sporocysts can be seen in their crushed tissues, and neither technique is capable of detecting a miracidial penetration until at least three weeks after the event. Since the lifetime of a snail, and in particular of a snail shedding cercariae, is relatively short compared with this three week delay, a substantial proportion of the snails which should be counted, to compute the proportion required for comparison with the model, may be missed. In this section, a catalytic model is used to show how to compensate for this discrepancy: cf. MUENCH (1959).

Consider a cohort of snails born at time 0, which have a natural death rate α. Suppose that the snails are also subject to infection at a rate μ, but that the infection remains latent for a fixed time a, during which the death rate remains as α, after which it becomes patent and the death rate increases to β. Let $x(t)$ denote the fraction of the initial population still alive and uninfected at time t (bearing in mind that $x(t) \to 0$ since no new uninfected snails arrive in the cohort), $y(t)$ the fraction alive and patently infected, and $z(t)$ the fraction alive and with latent infection, the remaining fraction $1 - x(t) - y(t) - z(t)$ being dead. Then the quantities x, y and z evolve according to differential equations, which are set out, with their solution, in Appendix 1.

Now consider a sample from the whole population of snails alive at any particular moment. If the sampling procedure does not differentiate between snails of different ages, and if the birth rate of snails is constant, the observed proportion of infected snails will estimate $Y/(X + Y + Z)$, whereas the actual proportion of infected snails, latent and patent, is $(Y + Z)/(X + Y + Z)$, where

$$X = \int_0^\infty x(t)\,dt;$$

$$Y = \int_0^\infty y(t)\,dt;$$

$$Z = \int_0^\infty z(t)\,dt.$$

The ratio $(Y + Z)/Y$, the factor by which the observed proportion of infected snails underestimates the actual proportion, comes out as

$$(2.1) \qquad 1 + \frac{\beta}{\alpha}(e^{\alpha a} - 1).$$

The quantities α, β and a can be directly observed, at least under laboratory conditions.

The assumption of constant death rates α and β for the snails implies negative exponential lifetime distributions; if this were observed to be far from the truth, time dependent rates $\alpha(t)$ and $\beta(t)$ could be introduced instead. Similar modifications could be made to allow for a variable length of latent period, seasonally varying birth rates, age sensitive sampling procedures, and the like. A stochastic model could also be used in the place of the deterministic one used here. However, under the most natural assumptions, the mean proportions in such a model are actually the same as those computed from the above formulation.

As an example of the possible magnitude of the correction factor (2.1), consider the parameter values $a = 9$ weeks, $\alpha^{-1} = 16$ weeks, $\beta^{-1} = 6$ weeks derived from data on *S. japonicum* at Malirong, published in PESIGAN *et al.* (1958b). These would lead to a correction factor of 3.0. The sampling procedures used to determine the proportion of infected snails in this study were, however, age sensitive, in that the ring method largely used was shown, by comparison with the tube method, to miss a substantial proportion of young snails, and also because, for the first two weeks of their life, the host snails were aquatic. Taking account of this information would reduce the factor by which the proportion of infected snails was underestimated to around 2.0. The proportions actually observed were normally between 0% and 6%, rising to as much as 40% in one locality in the rainy season. The steady state analysis given above would probably be appropriate for the low percentage figures, giving effective proportions of between 0% and 12%: the abrupt changes in conditions during the onset of the rainy season would need an analysis incorporating a time varying infection rate $\mu(t)$.

3. Heterogeneity

The effects of the latent period computed in the previous section may still not, in themselves, be enough to account for the low proportions of infected snails: indeed, even a true infection rate of 10% would leave relatively little apparent margin of stability at Malirong, though the disease seems nonetheless endemically stable. In this section, the importance of heterogeneity, amongst people and snails and also between seasons, is assessed.

The model in Section 1 is described in terms of parameters α, β, γ and δ, of which α and β in particular are defined as quantities intrinsic to the transmission cycle in the particular community. The first step in assessing the effects of heterogeneity in the system is to express α and β in terms of quantities which can be more easily compared between communities. A reasonable attempt at this would seem to be to assume that the density of miracidia in a particular piece of water was proportional to the product of the human population density, the number of female schistosomes per person, and the amount of contact with the water per person per day; and that the rate at which new snail infections occurred per unit area of water was proportional to the product of the density of miracidia, the proportion of uninfected snails, and possibly some function of snail density which would reflect the efficiency of miracidia in finding a snail host at different snail densities, and which, at all but very low snail densities, could probably be ignored. Similarly, the rate of increase in the female schistosome population within the human host population might be proportional to the product of the density of infected snails, the amount of water contact per person per day, and the size of the human population. These assumptions would give differential equations for $x(t)$ and $y(t)$, defined as in Section 1, similar to Equations (1.2):

$$(3.1) \qquad \dot{x} = \alpha\sigma y - \gamma x; \qquad \dot{y} = \beta x(1 - y) - \delta y;$$

where α and β now depend only on individual water contact rates, and where σ denotes the density of the human population. Here, and throughout the section, densities are with respect to accessible water area. Since Equations (3.1) are identical with (1.2), but for replacing α with $\alpha\sigma$, their qualitative behaviour is exactly the same. The threshold parameter η now becomes $\alpha\beta\sigma/\gamma\delta$, and the endemic equilibrium is given by

$$(\bar{x}, \bar{y}) = \left(\frac{\alpha\sigma}{\gamma}\left(1 - \frac{1}{\eta}\right),\ 1 - \frac{1}{\eta}\right),$$

leading, for instance, to an average worm burden per human host of

$$\bar{x}\rho/\sigma = \frac{\alpha\rho}{\gamma}(1 - 1/\eta),$$

where ρ is the snail population density.

If individual and spatial heterogeneity within the community is to be taken into account, the following extension of Macdonald's model seems appropriate. Suppose that the community consists of M people living in an area where there are L ponds, and that person i spends an amount of time λ_{ij} per day in pond j, where the snail density is ρ_j and the accessible water area A_j. Then the universal contact rates α and β are plausibly replaced by a set of rates $\alpha_{ij} = \alpha\lambda_{ij}$, $\beta_{ij} = \beta\lambda_{ij}$, and Equations (3.1) by the following system of equations for $[X_i(t)]_{i=1}$, the number of female schistosomes within person i, and $[Y_j(t)]_{j=1}$, the number of infected snails in pond i:

$$(3.2) \qquad \dot{X}_i = \alpha \sum_{j=1}^{L} \lambda_{ij} Y_j/A_j - \gamma X_i;$$

$$\dot{Y}_j = \beta \sum_{i=1}^{M} X_i \lambda_{ij}(1 - Y_j/\rho_j A_j) - \delta Y_j.$$

Note that, under the homogeneous mixing assumptions of $\rho_j = \rho$ for all j and $\lambda_{ij} = A_j/A$ for all i and j, where $A = \sum_{i=1} A_j$, these equations can be combined to yield equations (3.1) for $x = \sum_{j=1} X_i/N$, $y = \sum_{j=1} Y_i/N$, where $N = \rho A$ is the total number of snails in the community. Note also that, in what follows, spatial effects arising from continuous variation in conditions rather than from variation between a discrete set of ponds can be dealt with in an entirely similar way.

It is now no longer possible, in general, to derive an explicit expression for the equilibrium solution of (3.2), but there are some interesting things which can nonetheless be deduced from the equations. First, there is an immediate generalization of the threshold parameter η as the largest eigenvalue μ of a transmission matrix given in (2) of Appendix 2. The value of μ determines whether or not an endemic situation is possible: as with η in the simple model, stable transmission is not possible unless $\mu > 1$. Now μ may differ from one set of water contact rates λ_{ij} to another, even when the total water contact rate $\sum_{ij} \lambda_{ij}$ in the community remains constant, and it turns out that, among all possible choices of the λ_{ij}, the lowest value of μ is given by homogeneous mixing.

Thus if, in reality, mixing is not homogeneous, the true value of the threshold parameter μ will normally exceed the value corresponding to homogeneous mixing with the same total amount of water contact, and the disease will be more stable against changes in the under-lying parameters than might otherwise have been expected.

Unlike the threshold parameter μ, the total equilibrium schistosome burden in the community depends on the snail densities ρ_j, and in a rather complicated way. Even when ρ_j is the same for all ponds, it is not necessarily true that homogeneous mixing leads to the lowest schistosome burden for given amount of water contact. However, provided that $\rho_j = \rho$ for all j, it can be shown that homogeneous mixing gives a stationary value of the total schistosome burden which is locally almost a minimum: see Appendix 2(ii).

The implications of spatial heterogeneity for control purposes are complicated by the difficulty of observing the individual transmission parameters (λ_{ij}): it may often be the case that the quantities p_j, ρ_j, and A_j for the different ponds are the only available data. However, progress is possible if the simplifying assumption can be made that $\lambda_{ij} = \theta_i \lambda_j$: this assumption is equivalent to requiring that the *relative proportions* of time spent exposed at different ponds do not vary from person to person, though the *total* amounts of exposure may differ. Equilibrium estimates for certain combinations of the parameters can then be derived, as follows:

$$(3.3)\quad \lambda_j = [p_j \rho_j A_j/(1-p_j)]\left[\sum_{k=1}^{L} p_k \rho_k A_k/(1-p_k)\right]^{-1},$$

$$(3.4)\quad \frac{\alpha\beta}{\gamma\delta}\sum_{i=1}^{M}\theta_i^2 = \frac{\left[\sum_{j=1}^{L} p_j \rho_j A_j/(1-p_j)\right]^2}{\left[\sum_{j=1}^{L} p_j^2 \rho_j^2 A_j/(1-p_j)\right]},$$

$$(3.5)\quad \mu = \frac{\alpha\beta}{\gamma\delta}\left(\sum_{i=1}^{M}\theta_i^2\right)\left(\sum_{j=1}^{L}\lambda_j^2/A_j\right) = \frac{\left[\sum_{j=1}^{L} p_j^2 \rho_j^2 A_j/(1-p_j)^2\right]}{\left[\sum_{j=1}^{L} p_j^2 \rho_j^2 A_j/(1-p_j)\right]}.$$

Suppose now that eradication was to be attempted by keeping a number of ponds disease free, at a cost per pond of C per unit accessible water area. The effect on μ of treating ponds 1, 2, ..., k would be to remove the terms λ_j^2/A_j, $1 \leqslant j \leqslant k$, from the sum $\sum_j \lambda_j^2/A_j$ in (3·5), at a cost of $C.\sum_{j=1} A_j$. Thus it is most economical in general to reduce the threshold by treating those ponds for which λ_j^2/A_j^2 is largest, i.e. for which $p_j\rho_j/(1-p_j)$ is largest: note that, if ρ_j is the same for all ponds, this procedure is, as one would expect, exactly that of treating the most heavily infected ponds (in the sense of maximal p_j). Using (3.3), (3.4) and (3.5), it would be possible to determine which ponds should be treated to reduce μ to a specified value below unity with least cost, and to estimate what that cost would be.

An alternative procedure would be to attempt eradication by treating members of the human population as well. In an exactly similar way, an economical method would be to treat those people with largest over-all water contact rates θ_i. Note that only the ratios X_i/θ_i are expressible in terms of p_j, ρ_j and A_j, but that, within the terms of the model, the relative distribution of θ_i over the human population could be taken as being represented by the relative distribution of egg output rate. Then, knowing the cost of treating each person, an optimal combination of pond and human treatment could be found, by way of (3.3), (3.4) and (3.5). In practice, since the time scale for eradicating the disease in a community where not every human is treated will be of the order of the lifetime of an adult schistosome, and hence of an order significant in the social time scale of the human population, it would not necessarily be the same people who were treated throughout the programme: typically, high values could be expected in certain age groups within the population, such as teenagers and, over a ten-year period, the people within the age group would change.

It should be mentioned that, in the model formulated above, the snail densities do not appear

explicitly in the threshold parameter, and so it is not obvious (from the model!) that eliminating the snail population would interrupt transmission. This is because, at the beginning of Section 3, miracidia were explicitly assumed to have the same chance of penetrating a snail, provided that the snail density was not too low, which is a reasonable assumption if miracidia actively search for their quarry. Naturally, at extremely low snail densities, this assumption would break down, and the threshold parameter would be reduced. The implication remains, nonetheless, that an all or nothing policy for snail control should be adopted in each pond: reducing the density by half, while lowering the over-all transmission levels, would not contribute significantly to *eradicating* the disease.

There is no way of telling from the observed values p_j, ρ_j and A_j alone whether or not the assumption $\lambda_{ij} = \theta_i \lambda_j$ is justified: the full range of (λ_{ij}) consistent with a given set of observation (p_j, ρ_j, A_j) is described in Appendix 2(iii). However, the threshold parameter μ takes its minimal value consistent with the observed p_j, ρ_j and A_j when λ_{ij} is of the form $\lambda_j\theta_i$, the minimal value being given by (3.5). Thus the simplifying assumption $\lambda_{ij} = \theta_i \lambda_j$ leads to an optimistic extreme value for μ. At the other extreme, one has the intuitive upper bound for μ, which can be established directly from (3.2), of

$$(3.6) \qquad \mu \leqslant \left(1 - \max_{1 \leqslant j \leqslant L} p_j\right)^{-1},$$

and this bound can also be attained.

In general, the difference between the true value of μ and that given in (3.5) is a measure of the heterogeneity of the values $(1 - p_j)^{-1}$ between ponds; if p_j is the same for all ponds, (3.5) and the upper bound (3·6) coincide. If the difference might not be negligible, for instance if the discrepancy between (3.5) and (3.6) is large, it may be necessary to make a more accurate estimate of μ by some means, for instance by direct measurement of (λ_{ij}). Knowing the values of X_i as well would be of no help in this context.

When $\rho_j = \rho$ for all j, standard inequalities can be used to show that the plausible average estimates

$$A^{-1} \sum_{j=1}^{L} A_j (1 - p_j)^{-1}$$

and

$$\left[1 - A^{-1} \sum_{j=1}^{L} A_j p_j\right]^{-1}$$

for the threshold parameter μ, if a homogeneous mixing model had been assumed as an approximation to (3.2), are both smaller than the lower bound given by (3.5) for possible values of μ consistent with p_j, ρ_j and A_j. Thus the assumption $\lambda_{ij} = \theta_i \lambda_j$ in general represents an improvement over homogeneous mixing for the purpose of estimating μ.

The data in PESIGAN *et al.* (1958b) provide an example of the effect of heterogeneity on the threshold parameter. Table I contains information on p_j and ρ_j for ten snail colonies at Malirong, taken from Tables XXIII and XLVII of the paper, together with a relative measure of A_j for the different colonies, roughly estimated from the map in Fig. 17.

For May-June 1954, the threshold parameter is computed, from (3.6) and (3.5), to lie between 1.045 and 1.050, and, for February-March 1956, between 1.60 and 1.64. The correction suggested at the end of Section 3, applied to the proportions of infected snails, would increase the May-June 1954 value to around 1.1; an estimate of the corresponding value for February-March 1956 would be 2.5. It is noticeable how close the upper and lower bounds for the threshold are in this case, indicating that those colonies with the highest proportion of infected snails are overwhelmingly responsible for transmission of the disease. Note also that homogeneous mixing threshold values would here be computed at around 1.03 and 1.20 respectively (uncorrected for latent period), so that the uneven spatial distribution is equivalent to a further factor of between 2 and 3 multiplying the average proportion of infected snails.

Table XLVII and Fig. 38 of PESIGAN *et al.* (1958b) actually give figures for the percentage of infected snails in fourteen different periods between May 1954 and March 1956, which show that high percentages of infected snails follow periods of high rainfall, apparently because, in wet weather, miracidia are more easily brought into contact with snails. The two periods chosen in Table I show the extremes of the percentages of infected snails during the annual cycle: percentages are high for around three months, and low for the remainder of the year. It is obvious from the size of the discrepancy between the threshold values obtained in the two periods that seasonal heterogeneity should also be allowed for in the model, if the threshold parameter is to have any useful meaning. Because adult schistosomes have a relatively long life span, it is reasonable to suppose that the number of schistosomes in the human population does not vary much during the year. Then, letting β_1 and β_2 represent the human to snail transmission rates in the high and low transmission periods, t_1 and t_2 the proportion of the year for which each period lasts, and y_1 and y_2 the corresponding proportions of infected snails, supposed to have reached equilibrium with respect to β_1 and β_2, one gets three equations analogous to (1.3):

$$(3.7) \qquad \begin{aligned} \gamma x &= \alpha t_1 y_1 + \alpha t_2 y_2; \\ \beta_1 x(1 - y_1) &= \delta y_1; \\ \beta_2 x(1 - y_2) &= \delta y_2. \end{aligned}$$

The threshold parameter, given by the net reproductive rate per worm when $y_1 = y_2 = 0$, comes out to be $(\alpha/\gamma\delta)(\beta_1 t_1 + \beta_2 t_2)$, which, from (3.7), can be expressed in terms of observable quantities as

$$(3.8)\qquad \left[\sum_{j=1}^{2} t_j y_j/(1-y_j)\right]\Big/\left[\sum_{j=1}^{2} t_j y_j\right].$$

Taking the corrected values $y_1 = 0.6$, $y_2 = 0.09$, together with $t_1 = 0.25$, $t_2 = 0.75$, gives a threshold of 2.07, equivalent to 50% of infected snails in a homogeneous system. Again, a better estimate of the threshold parameter is given by taking the largest value among the possible choices than by taking the average value, indicating that most of the year's transmission takes place around the wet season.

Formula (3.8) has an immediate generalization if there are more than two distinct transmission periods per year. Furthermore, the inequalities

$$\left[\sum_{j=1}^{n} t_j y_j/(1-y_j)\right]\Big/\left[\sum_{j=1}^{n} t_j y_j\right] \geqslant \left[\sum_{j=1}^{n} t_j/(1-y_j)\right]\Big/\left[\sum_{j=1}^{n} t_j\right] \geqslant \left[1-\left(\sum_{j=1}^{n} t_j y_j\right)\Big/\left(\sum_{j=1}^{n} t_j\right)\right]^{-1}$$

show that, once again, averages based on the assumption of a homogeneous model give too small an estimate of the threshold parameter.

4. The response to infection of the human host

Macdonald's model singles out the proportion of infected snails as the key factor in controlling the transmission cycle of bilharzia. If, even allowing for the corrections mentioned so far, the threshold parameter still seems too low, other possible controlling factors should be investigated. One possibility is that the schistosomes in a human host influence his response to further infection, for instance by encouraging an immune response or because of crowding effects which lead to decreased egg output per female schistosome.

There is some evidence in favour of such a response given by age-prevalence curves. If the sequence of times at which a human host is infected by groups of one or more cercariae arise as a Poisson process of constant rate, and if the lifetimes of different schistosomes are independent, the age-prevalence curves in a demographically stable community should increase monotonically to an eventual limit. This is in contrast with the curves peaking at around age 15 years and then settling around a lower limit which are often observed in practice: see, for example, JORDAN & WEBBE (1969), pp. 151-158. A similar phenomenon in relation to egg output is observed in PESIGAN *et al.* (1958a). One explanation which would account for these curves is that, because of changing social habits, the infection rate is not constant over all age groups; however, similar curves are observed even among adult populations which have recently immigrated into infected areas (KLOETZEL & DA SILVA (1967)), so this explanation may only furnish part of the truth. Certain models allowing partial or complete temporary immunity are also capable of producing curves of the observed form, as for instance in LEWIS (1974), though the conditions for this are not entirely clear. For instance, a Markov model based on the constant rate Poisson model above, but in which the infection rate is lower for presently infected hosts, still gives monotone age-prevalence curves, whereas a model in which a person, once infected, remains infected for a fixed period, and then becomes uninfected and susceptible again, gives curves of the observed form. Nonetheless, an immune response could be at least partly responsible for the shape of the age-prevalence curves.

To get some idea of the effect on the Macdonald model of incorporating human immunity in the system, suppose that an individual, once infected, remains infected for a length of time negative exponentially distributed with parameter ψ, during which he is immune to further infection, and then becomes susceptible again (note that these assumptions are not only somewhat implausible, but would still lead to monotone age-prevalence curves). Then, constructing a model along the lines followed in Section 1, one arrives at differential equations for x, the proportion of the human population infected, and y, the proportion of the snail population infected, as follows:

$$(4.1)\qquad \dot{x} = \alpha\phi y(1-x) - \psi x; \qquad \dot{y} = \beta\phi^{-1} x(1-y) - \delta y,$$

where ψ is defined above, α, β and δ are as in Section 1, and ϕ is the ratio of the number of snails to the number of human beings in the community. There is, as before, a threshold parameter $\eta' \equiv \alpha\beta/\psi\delta$, and an endemic state is only possible if $\eta' > 1$: in this case, the endemic equilibrium is given by

$$(4.2)\qquad \bar{x} = (1 - 1/\eta')/(1 + \psi/\alpha\phi); \qquad \bar{y} = (1 - 1/\eta')/(1 + \phi\delta/\beta).$$

These two equations can be solved for the ratios $\psi/\alpha\phi$ and $\phi\delta/\beta$, whose product is $1/\eta'$, giving

$$(4.3)\qquad \phi\delta/\beta = \bar{x}(1/\bar{y} - 1); \quad \psi/\alpha\phi = \bar{y}(1/\bar{x} - 1); \quad \eta' = [(1-\bar{y})(1-\bar{x})]^{-1}.$$

Comparing (4.2) with (1.3), it can be seen that $\phi\delta/\beta$ small and $\psi/\alpha\phi$ large corresponds to a situation where Macdonald's snail factor is what limits the transmission cycle; conversely, with $\phi\delta/\beta$ large and $\psi/\alpha\phi$ small, human immunity is the important limiting factor. So if $\bar{y}$, even allowing for the corrections indicated in the earlier sections, were

small, and if $\bar{x}$, the overall prevalence in the human population, were around 50% or more, a reasonable first estimate of η' would be given by $(1-\bar{x})^{-1}$, and not $(1-\bar{y})^{-1}$ as suggested by Macdonald's model. Under these conditions, any attempt at a more precise determination of η' would require a more sophisticated model than that given in (4.1): the simplistic biological assumptions might reasonably be retained without making too serious a difference, but the varying social habits of the different members of the human population are likely to be very significant as far as effects summarised by $\bar{x}$ are concerned, and a treatment along the lines of Section 3 would probably be needed.

PESIGAN *et al.* (1958a, b) give values of $\bar{x}$ of around 0.8 for the area near Malirong, compared with the value 0.5 for $\bar{y}$ which is arrived at after the adjustments in Sections 2 and 3. These values would give $\phi\delta/\beta = 0.8$, $\psi/\alpha\phi = 0.125$, $\eta' = 10.0$. The threshold value of 10 seems more plausible even than the value of 2 computed in Section 3, for a community where the disease is highly stable. The above analysis also suggests that human immunity is the more important factor in limiting the severity of the disease.

The implications of this model in relation to eradication of bilharzia are not very different from those of Macdonald's model, except in so far as a better estimate of the threshold parameter is obtained: the dependence of the threshold parameter on the transmission parameters is as before. For control, if eradication proves impracticable, it would be more effective, from the point of view of reducing total schistosome burden, to treat the human population (thus reducing the number who were susceptible to infection) than to reduce the snail population, if human immunity was the important limiting factor; whereas, in the opposite case, snail control would be preferable.

5. Conclusion

The main aim of the paper has been to show that, for Macdonald's model of the transmission of bilharzia to be compatible with observation, it must be seen as a simple approximation to a more complicated phenomenon, and to deduce, from the more complicated models, ways in which appropriate parameter estimates for the simple model may be arrived at. The features on which most emphasis has been placed are the estimation of the threshold parameter and the limiting of the transmission cycle by the proportion of infected snails. In Section 4, in particular, it is shown how, in an alternative simple model allowing for human immunity, the data of PESIGAN *et al.* (1958a, b) for Malirong are consistent with a much more stable endemic situation than can be obtained from Macdonald's model. This suggests that, without further biological evidence to discriminate between such models, cost effective control must be governed largely by empirical considerations, since the discrepancy between the threshold values obtained under the two different models is so great. It is tempting to take the endemic stability of bilharzia at Malirong as evidence in favour of the model incorporating human immunity, but it is hardly conclusive evidence: the final value arrived at for the threshold parameter under Macdonald's model was still quite large.

The direction taken in the paper has bypassed a number of phenomena, many of them mathematically interesting, many of them already investigated elsewhere. Animal reservoirs of infection are not directly considered, though the treatment in Section 3 is sufficiently general to allow definitive hosts to be other than human; in particular, the empirical bounds (3.6) and (3.5) remain unchanged. Absent also are the various stochastic effects—the sexual behaviour of schistosomes, the number of cercariae penetrating at one infection, the random behaviour of human beings and so on—which would be of essential importance in estimating the distribution of the numbers of schistosomes in a human host or the chance of an infected person introducing infection into a new area. Since infection with *S. japonicum* may typically be by rather few schistosomes (HAIRSTON (1962)), the conclusions derived from the data in PESIGAN *et al.* (1958a, b) by the methods of Sections 3 and 4 should perhaps be treated with some care, though the particular aspects considered seem relatively insensitive to such effects. In any case, the results should still provide useful indications of what can be expected in general, as well as highlighting important features of the particular local transmission cycle.

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Appendix 1

The differential equations governing the evolution of x(t), y(t) and z(t) in the catalytic model of Section 2 are

$$\begin{aligned} dx(t)/dt &= -(\alpha+\mu)\,x(t) \\ dz(t)/dt &= \mu x(t) - \alpha z(t) - \mu\, e^{-\alpha a}\, H(t-a)\, x(t-a) \\ dy(t)/dt &= \mu\, e^{-\alpha a}\, H(t-a)\, x(t-a) - \beta y(t), \end{aligned} \tag{1}$$

where

$$H(x) = \begin{cases} 1 & \text{if } x \geqslant 0 \\ 0 & \text{if } x < 0. \end{cases}$$

The proportion of snails alive at time t which are observable as infected is then $p(t)=y(t)/[x(t)+y(t)+z(t)]$, whereas the proportion infected is actually $q(t)=[y(t)+z(t)]/[x(t)+y(t)+z(t)]$. Solving (1), one obtains

$$x(t) = e^{-(\alpha+\mu)t}$$

$$z(t) = \begin{cases} (e^{\mu t}-1)\, e^{-(\alpha+\mu)t}, & t \leqslant a \\ (e^{\mu a}-1)\, e^{-(\alpha+\mu)t}, & t > a \end{cases}$$

$$y(t) = \mu\, e^{-\alpha a}\,[e^{-\beta(t-a)} - e^{-(\alpha+\mu)(t-a)}] \times (\alpha+\mu-\beta)^{-1}\, H(t-a),$$

from which expressions for p(t) and q(t) can be deduced. Both p and q are increasing functions of t, and, as $t \to \infty$,

$$p(t) \to 1 \quad \text{and} \quad q(t) \to 1 \quad \text{if} \quad \beta \leqslant \alpha + \mu,$$
$$p(t) \to \mu/(\beta - \alpha) \text{ and } q(t) \to 1 - e^{-\mu a}(1 - \mu/(\beta - \alpha)) \quad \text{if} \quad \beta > \alpha + \mu.$$

It is possible to observe α, β and a, at least under laboratory conditions, and μ is then in principle estimable by fitting the curve for p(t) to empirical values of the proportions of snails of various ages observed to be infected.

Appendix 2
Mathematical treatment of Section 3

(i) *The threshold parameter*

A non-zero equilibrium solution to (3.2) can occur if and only if the linear approximation to (3.2) near the origin,

$$\begin{aligned} \dot{X}_i &= \alpha \sum_j \lambda_{ij} Y_j/A_j - \gamma X_i; \\ \dot{Y}_j &= \beta \sum_i X_i \lambda_{ij} - \delta Y_j, \end{aligned} \tag{1}$$

is unstable. Standard manipulation equates this to the requirement that the Perron-Frobenius eigenvalue μ of the LxL matrix U with components

$$U_{jk} = \frac{\alpha\beta}{\gamma\delta} A_j^{-1} \sum_i \lambda_{ij} \lambda_{ik} \tag{2}$$

be greater than unity: μ is thus the natural generalization of the threshold parameter η. If α and β are to be identified as over-all average water contact rates per person, the elements λ_{ij} must be standardised by the requirement that $\sum_{i,j} \lambda_{ij} = M$. Under this restriction, μ is minimized among possible choices of (λ_{ij}) by the homogeneous mixing choice $\lambda_{ij} = A_j/A$, for which $\mu = \alpha\beta\sigma/\gamma\delta$, where $\sigma = M/A$. This can be seen as follows. Suppose that x is an eigenvector of U with eigenvalue p, so that $Ux = px$. Then the vector y with $y_j = x_j A_j^{1/2}$ satisfies $Vy = py$, where

$$V_{jk} = (\alpha\beta/\gamma\delta) A_j^{-1/2} \sum_i \lambda_{ij} \lambda_{ik} A_k^{-1/2}. \tag{3}$$

V is symmetric, and so its largest eigenvalue, hence also that of U, is given by

$$\max_{y'y=1} y' Vy.$$

Now the choice $y_j = (A_j/A)^{1/2}$, $j = 1, \ldots, L$, gives $y'y = 1$ and

$$y' Vy = (\alpha\beta/\gamma\delta A) \sum_i \left(\sum_k \lambda_{ik} \right)^2 \geqslant M\alpha\beta/\gamma\delta A,$$

this last because $\sum_{i,j} \lambda_{ij} = M$. Hence the Perron-Frobenius eigenvalue of U is always at least $\alpha\beta\sigma/\gamma\delta$, and takes this value exactly if $\lambda_{ij} = A_j/A$, which is the case of homogeneous mixing. μ also attains this value if $\lambda_{ij} = A_j/A + \epsilon_{ij}$, provided that $\sum_{k=1}^{M} \epsilon_{kj} = \sum_{k=1}^{L} \epsilon_{ik} = 0$ for all i and j.

(ii) *Equilibrium schistosome burden*

As an example to illustrate that homogeneous mixing does not necessarily lead to the lowest schistosome burden for given amount of water contact, consider a community in which $L = M$, $A_j = a$, $\lambda_{ij} = 0$ if $i \neq j$, and $\alpha\beta/\gamma\delta a = 2$: then, if $\lambda_{ii} \geqslant 1/\sqrt{2}$.

$$X_i = \rho \frac{\alpha}{\gamma} (\lambda_{ii} - 1/2\lambda_{ii}), \quad 1 \leqslant i \leqslant M,$$

and so

$$\sum_i X_i = \rho \frac{\alpha}{\gamma} \left(M - \sum_i 1/2\lambda_{ii} \right).$$

Choosing

$$\begin{aligned} \lambda_{11} &= M - (M-1)/\sqrt{2}, \\ \lambda_{ii} &= 1/\sqrt{2}, \; 2 \leqslant i \leqslant M, \end{aligned}$$

gives

$$\frac{1}{M} \sum_i X_i = \rho \frac{\alpha}{\gamma} (1 - 1/\sqrt{2}) + O(M^{-1}), \quad \text{as } M \to \infty,$$

compared with the larger homogeneous mixing burden of $\rho\alpha/2\gamma$.

If perturbations of the form $\lambda_{ij} = A_j/A + \epsilon_{ij}$ are considered, where $\|\epsilon\|$ is small and $\sum_{i,j} \epsilon_{ij} = 0$, the total schistosome burden can be expressed as

$$\begin{aligned} \sum_{i=1}^{M} X_i = \rho \frac{\alpha}{\gamma} \Bigg[& M(1 - 1/\eta) \\ & + (A\delta/\beta M\eta^2) \sum_{j=1}^{L} \epsilon_{\cdot j}^2/A_j + \eta^{-1} \sum_{i=1}^{M} \epsilon_{i\cdot}^2 \Bigg] \\ & + o(\|\epsilon\|^2), \end{aligned} \tag{4}$$

where $\epsilon_{i\cdot} \equiv \sum_{k=1}^{L} \epsilon_{ik}$, $\epsilon_{\cdot j} \equiv \sum_{k=1}^{M} \epsilon_{kj}$. This indicates that homogeneous mixing yields a locally minimal schistosome burden, at least to order $\|\epsilon\|^2$; once again, perturbations (ϵ_{ij}) for which $\epsilon_{i\cdot} = \epsilon_{\cdot j} = 0$ have no effect.

(iii) *Parameter estimation from* p_j, ρ_j *and* A_j.

Consider first the case when $\lambda_{ij} = \theta_i \lambda_j$. Then without loss of generality, we can take $\sum_j \lambda_j = 1$, so that the overall constraint on the amount of water contact reduces to $\sum_i \theta_i = M$. Equations (3.2) then reduce, in equilibrium, to

$$(5) \qquad X_i = (\alpha/\gamma)\,\theta_i \sum_{j=1}^{L} \lambda_j\, Y_j/A_j$$

and

$$(6) \qquad Y_j(1 - Y_j/\rho_j\, A_j)^{-1} = (\beta/\delta)\,\lambda_j \sum_{i=1}^{M} \theta_i\, X_i;$$

p_j, ρ_j and A_j are assumed known, whence $Y_j = p_j\, \rho_j\, A_j$ also, and there are the constraints

$$(7) \qquad \sum_{j=1}^{L} \lambda_j = 1. \qquad \sum_{i=1}^{M} \theta_i = M.$$

It follows from (6) that

$$\lambda_j \propto p_j\, \rho_j\, A_j/(1 - p_j),$$

and so, from (7)

$$(8) \quad \lambda_j = [p_j\, \rho_j\, A_j/(1 - p_j)]\left[\sum_{k=1}^{L} p_k\, \rho_k\, A_k/(1 - p_k)\right]^{-1};$$

hence also, from (6),

$$(9) \qquad (\beta/\delta) \sum_{i=1}^{M} \theta_i\, X_i = \sum_{k=1}^{L} p_k\, \rho_k\, A_k/(1 - p_k).$$

The values of λ_j obtained in (8) can now be substituted into (5) to give an expression for X_i/θ_i: in particular, multiplying the i^{th} member of (5) by θ_i and summing over i gives, using (9),

$$(10) \qquad \frac{\alpha\beta}{\gamma\delta} \sum_{i=1}^{M} \theta_i^2 = \frac{\left[\sum_{j=1}^{L} p_j\, \rho_j\, A_j/(1 - p_j)\right]^2}{\left[\sum_{j=1}^{L} p_j^2\, \rho_j^2\, A_j/(1 - p_j)\right]}$$

Since also, if $\lambda_{ij} = \theta_i\, \lambda_j$, the threshold eigenvalue μ is given by

$$(11) \qquad \mu = \frac{\alpha\beta}{\gamma\delta}\left(\sum_{i=1}^{M} \theta_i^2\right)\left(\sum_{j=1}^{L} \lambda_j^2/A_j\right),$$

it can be directly expressed in terms of p_j, ρ_j and A_j, through (10) and (8), as

$$(12) \qquad \mu = \frac{\left[\sum_{j=1}^{L} p_j^2\, \rho_j^2\, A_j/(1 - p_j)^2\right]}{\left[\sum_{j=1}^{L} p_j^2\, \rho_j^2\, A_j/(1 - p_j)\right]}.$$

To find the full range of parameters consistent with the observed values of p_j, ρ_j and A_j, let $\Lambda = (\lambda_{ij})$ and α, β, γ and δ be any transmission parameters giving rise to these values. Define $r_j = p_j\, \rho_j$, $s_j = A_j/(1 - p_j)$, and, as in (8), set

$$\lambda_j = r_j\, s_j \Big/ \sum_{k=1}^{L} r_k\, s_k;$$

let R denote the right hand side of (10), and write

$$(13) \qquad \lambda_{ij} = \theta_i\, \lambda_j + \epsilon_{ij} \geqslant 0,$$

where

$$(14) \qquad \theta_i = \sum_{j=1}^{L} \lambda_{ij}\, r_j \Big/ \sum_{j=1}^{L} \lambda_j\, r_j;$$

note that, in consequence,

$$(15) \qquad \sum_{j=1}^{L} \epsilon_{ij}\, r_j = 0, \qquad 1 \leqslant i \leqslant M.$$

Now if Λ, α, β, γ and δ are to give the particular values p_j, ρ_j and A_j, it follows, solving (3.2) in equilibrium, that

$$(16) \qquad \frac{\alpha\beta}{\gamma\delta} \sum_{i=1}^{M} \sum_{k=1}^{L} \lambda_{ij}\, \lambda_{ik}\, r_k = r_j\, s_j, \qquad 1 \leqslant j \leqslant L.$$

Substituting for λ_{ij} from (13) and using (14), Equation (16) can be re-expressed as

$$(17) \qquad r_j\, s_j = R^*\, R^{-1}\, r_j\, s_j + \frac{\alpha\beta}{\gamma\delta} \sum_{k=1}^{L} \lambda_k\, r_k \sum_{i=1}^{M} \theta_i\, \epsilon_{ij}, \qquad 1 \leqslant j \leqslant L,$$

where

$$R^* \equiv \frac{\alpha\beta}{\gamma\delta} \sum_i \theta_i^2.$$

Multiplying the jth equation of (17) by r_j and adding over j gives

$$(18) \qquad \left(\sum_{j=1}^{L} r_j^2\, s_j\right)(1 - R^*/R) = 0,$$

because of (15); hence $R^* = R$, i.e. (10) holds, and

$$(19) \qquad \sum_{i=1}^{M} \theta_i\, \epsilon_{ij} = 0, \qquad 1 \leqslant j \leqslant L.$$

Thus any Λ, α, β, γ and δ giving rise to the observed values of p_j, ρ_j and A_j must be consistent with (10), (13), (15) and (19); it is easy to show conversely that any choice of θ_i, ϵ_{ij} and α, β, γ, δ satisfying (10), (13), (15) and (19) gives the specified values of p_j, ρ_j and A_j.

For any such choice, the matrix U of (2) can be written as

$$(20) \qquad U_{jk} = \frac{\alpha\beta}{\gamma\delta} A_j^{-1} \left[\lambda_j \lambda_k \sum_{i=1}^{M} \theta_i^2 + \sum_{i=1}^{M} \epsilon_{ij} \epsilon_{ik} \right],$$

from which it follows that the threshold parameter μ takes its minimal value consistent with the observed p_j, ρ_j and A_j when $\epsilon_{ij} = 0$ for all i and j, the minimal value being given by (12).

The method leading up to (20) carried over to many phenomena which are maintained by intermixing. Indeed, if $\Lambda = (\lambda_{ij})$ is an unknown MxL matrix of non-negative numbers which is known to satisfy the L equations.

$$(21) \qquad a_j = \sum_k \lambda_{ij} \lambda_{ik} b_k, \qquad 1 \leqslant j \leqslant L,$$

where $(a_j, b_j)_{j=1}^{L}$ are known non-negative quantities then any matrix Λ of the form $\lambda_{ij} = \theta_i \lambda_j$ consistent with (21) gives rise to the minimum possible value of the largest eigenvalue of any matrix of the form $A^T \Lambda^T \Lambda A$. Equations (21) are typical of the equilibrium conditions for a disease maintained by intermixing, and the value of the largest eigenvalue of a matrix of the form $A^T \Lambda^T \Lambda A$ will often determine whether or not the disease can become endemic.

(*iv*) *The upper bound* (3.6)

An example, in which the upper bound (3.6) for values of μ consistent with (p_j, ρ_j, A_j) is attained, is constructed as follows. Take

$$\lambda_{11} = [\gamma\delta A_1 / \alpha\beta(1 - p_1)]^{1/2}$$
$$\lambda_{1j} = 0, \quad j \neq 1:$$
$$\lambda_{i1} = 0, \quad i \neq 1:$$

where $\max_j p_j$ is assumed, without loss of generality, to be attained at $j = 1$: the remaining values of λ_{ij} can then be taken to be any set consistent with the data p_j, ρ_j, A_j, $2 \leqslant j \leqslant L$. The construction yields values of λ_{ij} which do not necessarily satisfy the standardisation constraint $\sum_{i,j} \lambda_{ij} = M$, but this can be achieved if α and β are adjusted in compensation. The resulting transmission scheme is degenerate, in the sense that person 1 and pond 1 form an isolated community within the larger group, but, by standard continuity arguments, a community with no completely isolated sub-communities can be constructed with μ arbitarily close to the maximum given in (3.6).

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