6 Schistosomiasis

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6.1 INTRODUCTION

Schistosomiasis is a parasitic disease which is widespread in the tropics. The parasites, schistosomes, are digenetic trematodes, which normally inhabit the veins around the bladder or bowel. There are three principal varieties of human schistosome, each with its own peculiarities, broadly corresponding to the different continents in which the disease is found: *Schistosoma haematobium*, which is found throughout North and Central Africa, *Schistosoma mansoni*, found mainly in South America and Central Africa, and *Schistosoma japonicum*, which is found in China, Japan and the Philippines. Their life cycles are, however, sufficiently similar for them to be treated in the same way when building qualitative models of the transmission of the disease, even though the parameters in the models may differ substantially from one species to another; the following brief account of their natural history applies in general to all three. A detailed description of most aspects of the disease is given in the excellent book by Jordan and Webbe (1969).

The full life cycle of a schistosome involves two hosts, one human and the other an aquatic snail. A diagrammatic representation of the cycle is depicted in Fig. 6.1. Adult schistosomes live in pairs within their human hosts for a span of several years, during which time they steadily produce eggs. Many of the eggs, perhaps as many as 90% or more (Nelson and Saoud, 1966), fail to complete their intended migration to the bladder or bowel, and become lodged in tissues elsewhere in the body, inducing more or less serious damage. Of the remainder, a proportion of those that reach water after excretion hatch into microscopic free-swimming miracidia. Each miracidium has a life span of around 1 day, which it spends searching for a snail host of the right variety; it is capable of recognizing an attractant secreted by the snail, and of locating it by swimming in a direction of increasing concentration of attractant. The miracidium penetrates the soft tissues of the snail, and initiates a process of asexual multiplication, which eventually results in hundreds of free-swimming cercariae, all of the same sex, being released into the water. The length of time that elapses between miracidial infection and the first release of cercariae is of the order of several weeks (roughly 5 weeks), and cercariae then continue to be released until the death of the snail (Anderson and May, 1979b). Cercariae, which, like miracidia, only live for a day or so, are also capable of locating their potential hosts, apparently by recognizing disturbance of the water surface,

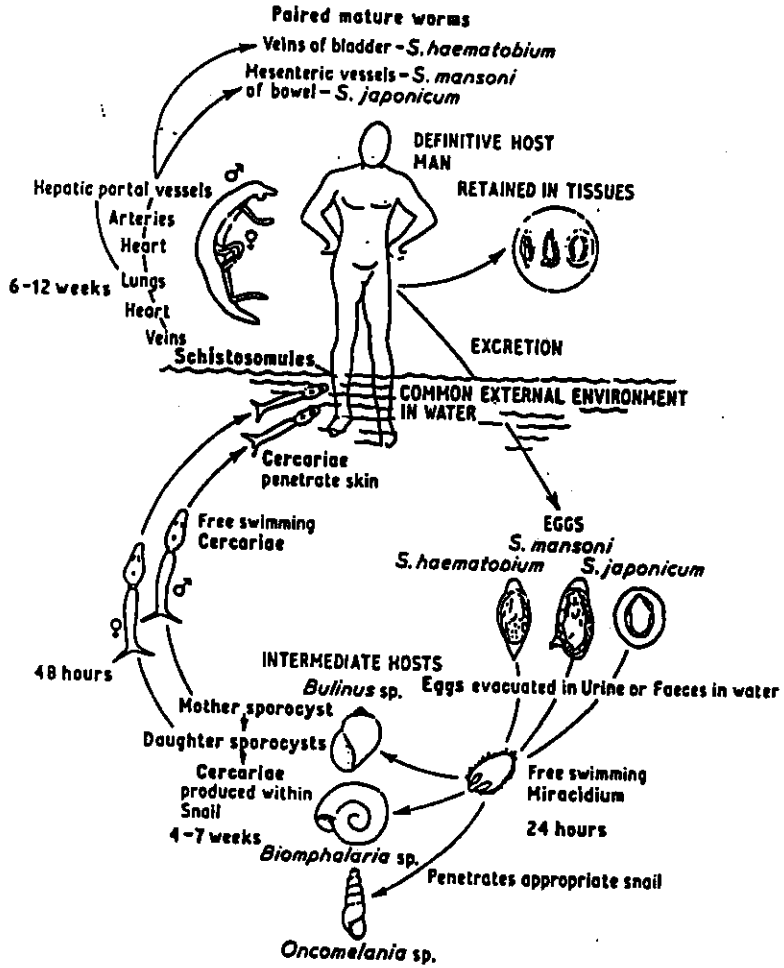

Figure 6.1 A diagrammatic representation of the life cycle of human schistosomes showing the two host species involved (man and snail) and the various developmental stages of the parasite (from Jordan and Webbe, 1969).

and enter the body through any skin exposed under water (Fig. 6.2). They then migrate via the lungs to the liver, where they develop into adult schistosomes, mate, and depart to their final home, in the mesenteric veins or the terminal venules of the vesical plexus, to lay their eggs, the whole phase of development within the human host lasting for 6 or more weeks.

One of the most awkward problems in gathering biological information about the disease is that it is virtually impossible to obtain any detail about schistosomes within the human host. For instance, the only effective way of

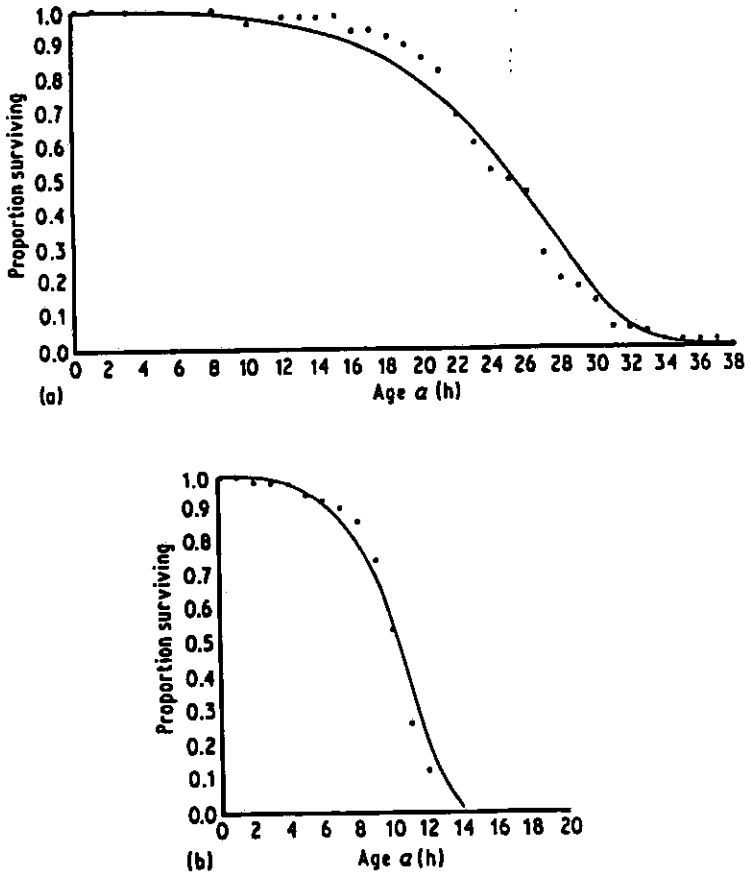

Figure 6.2 Survival of the cercaria and miracidium of *Schistosoma mansoni* at 25 °C. (a) The survival of the cercarial stage. Solid points, observed proportion of cohort surviving at age t; solid line, best-fit age-dependent survival model. (Unpublished data, Anderson and Smith, Imperial College, London.) (b) The survival of the miracidial stage. Solid points and solid line as for (a). (Unpublished data, Anderson and Smith, Imperial College, London.)

determining the number of schistosomes living in a particular host, and their distribution around the body, is by dissection. Thus much of what is thought to take place within the human host relies on analogy with findings about schistosomes in other animal hosts, such as mice, on autopsy studies, which, in particular, are not suitable for measuring changes over time within a particular host, or on indirect measurements, such as of immunological reaction or of the rate of excretion of eggs. Questions about the life span of schistosomes and

about their mating habits, which could have a substantial influence on transmission, and hence on control, do not seem as yet to have reliable answers. Nor is it even possible, because of the character of the disease, to say in more than very general terms how serious are its effects, in comparison with those of other diseases, on the lives of the people exposed to it.

Perhaps the most surprising gap is the lack of information about immunity acquired by the human host. In any population system of this sort, there must be some mechanism that reduces the net reproductive rate as the population grows, because it readily develops in newly susceptible communities (i.e. has an initial net reproductive rate (R) greatly exceeding unity), but nonetheless subsequently attains an equilibrium within the community. Possible mechanisms within a parasitic system include *density-dependent* (crowding) effects induced by immune responses or competition for limited resources, within either host, increased host mortality and acquired host immunity. The classical explanation for schistosomiasis, advanced by Macdonald (1965), lies in the observation that a snail which has been infected by more than one miracidium releases cercariae no faster, and indeed sometimes slower, than a snail infected by precisely one miracidium. This rather extreme crowding effect implies that the total amount of infection that a community could sustain could be no greater than that fixed level which would result if its entire snail population were releasing cercariae at maximum rate. In practice, a lower level would be attained, because of the long (in terms of a snail's life) latent period of infection within the snail, and because the net reproductive rate in the system, which must be proportional to the chance that a successful miracidium has penetrated an as yet uninfected snail, must fall to its equilibrium value of unity before this chance reaches zero, which would be the case once all snails were infected. Increased snail mortality could possibly reinforce Macdonald's mechanism at high levels of transmission, if multiple miracidial infections tended to kill snails more quickly than single infections, but it seems unlikely that this is of any practical importance. Acquired immunity in snails is also unlikely to be significant, because of their short life span relative to the timescale of the transmission process, and it is, in any case, not observed. In the human host, increased mortality is difficult to assess, though it may, indirectly, play some part; but the long life span of the human host makes it unlikely to be very effective in controlling transmission. Crowding effects are, as indicated earlier, all but impossible either to substantiate or to disprove, and so must remain a possibility, though the apparent capability of some human hosts to sustain unusually large egg outputs perhaps tenuously suggests that such effects, if present, are not important in limiting transmission. There remains the possibility of acquired immunity in man. The importance of such a phenomenon for the control of schistosomiasis and the evidence for its existence are discussed in some detail later; it suffices for now to remark that no experiment has yet satisfactorily demonstrated the existence of such a mechanism in man.

6.2 A SIMPLE MATHEMATICAL MODEL

The earliest attempt to apply mathematical methods to explaining the transmission cycle of schistosomiasis was probably that of Hairston (1961), though its scope was rather limited. The first genuinely dynamic model of the system was proposed by Macdonald (1965), who used it to reach the celebrated conclusion that safe water supplies are more important than latrines. It is actually not easy to see how he could have reached this conclusion using only his model and the available data, and it is therefore very doubtful whether it should be accepted as an instance of the useful application of mathematics in epidemiology – it is rather more likely that it was a conclusion derived from a lifetime of experience in tropical medicine, and should properly be respected as such (see also Scott and Barlow, 1938). Macdonald's model is nonetheless the foundation for almost all subsequent models of transmission, and its essential importance lies in its clear statement of the mechanism of the effect of crowding within the snail host, which limits the reproductive capacity of the parasite population. Accepting this almost universal precedent, we shall start by considering a variant of Macdonald's model, in this case a rather simpler version, and then try to assess its success when considered in the light of the available data.

The basic model is derived by considering the flow of infection between man and snails in an isolated community. Starting with the flow from man to snail, it seems reasonable to suppose initially that the density of miracidia in the water around the locality should be proportional to a variety of different factors: the density of the human population, the number of egg-laying schistosomes per human host, the number of fertile eggs laid per schistosome per day, the chance of a given egg being excreted and reaching water, which itself is likely to be more or less related to the amount of water contact per person per day, and so on. Distinguishing each of these factors in the model would lead to very cumbersome expressions, and would very likely obscure its essential elements. Fortunately, many of them are, under Macdonald's assumptions, constant characteristics of the particular populations in question which are not materially influenced by the progress of transmission. For instance the human population density is not likely to vary greatly in response to different levels of infection, since schistosomiasis does not have too dramatic an effect on mortality, and the local inhabitants are not often willing or able to abandon infected areas. This is not intended to rule out the possibility of any dependence of the human population density upon the level of infection, but merely to propose that in an attempt at reasonable simplification of the model, it should be ignored as being less significant a feature of the transmission cycle than many others. Should there, however, be cause to suppose otherwise, or should this aspect be of particular interest for other reasons, as, for example, in May and Anderson (1979), it could then be explicitly incorporated into the model.

Making similar assumptions about some of the other factors mentioned above, we shall suppose that the density of miracidia is proportional to the ratio of the total number of egg-laying schistosomes in the population and the available water area. The constant of proportionality in the ratio depends only on the social habits of the human hosts, on biological parameters relating to the particular strain of the parasite, and on the local geography, but not on the level of infection or on the area of available water. Note that we are thereby implicitly assuming that the distribution of schistosomes within the human host population does not affect total egg output. Note also that constants of proportionality, such as the one discussed above, are normally the parts of the model that are affected by control measures. For example, providing safe water supplies for bathing and washing clothes might halve the amount of contact with hazardous water, and thereby reduce the constant of proportionality by half. If the model is to be useful, it should accommodate the effects of control measures within its existing structure. Just as biological reality may force one to abandon a simple model in favour of a more complex one, so may sometimes the need to describe the effects of particular control measures.

The next stage is to make some statement about how the density of miracidia is related to the rate at which snails are infected. Here, Macdonald's assumption about the effect of crowding within the snail host is introduced. It indicates that, for the purposes of transmission, it is the number of infected snails that is important, and not how often they have been infected, and hence that only miracidial penetrations of hitherto uninfected snails need to be taken into account. The simplest assumption, therefore, is to suppose that the rate at which new snail infections occur, per unit area of water, is proportional to the product of the density of miracidia, the chance that a given miracidium succeeds in penetrating a snail, and the chance that the snail penetrated was previously uninfected. This last is plausibly estimated as the current proportion of uninfected snails in the snail population, on the assumption that the miracidium does not distinguish between infected and uninfected snails. This is probably not strictly true, as the laboratory experiments of Disko and Weber (1979) would indicate, but should nonetheless constitute a reasonable first approximation. There remains the chance of successful penetration, which depends upon many environmental quantities, but principally, at least from a control point of view, upon the snail density. The particular form which the dependence takes in the field is not known, but, in view of the searching activity of the miracidium, it is reasonable to suppose that only at low snail densities does finding a snail present a problem, and that the chance of success is usually fairly close to its maximum value. Combining these assumptions, we arrive at an overall rate of new snail infections in the community of $\beta X q$, where X is the current total number of egg-laying schistosomes, q is the current proportion of uninfected snails, and β is a constant depending on biological, social and environmental factors, and which is susceptible to alteration by control

The rate of flow of infection between snails and man is modelled in a similar way. In view of Macdonald's assumption, the rate of acquisition of egg-laying schistosomes by the human host population should be proportional to the size of the human population, the amount of water contact per person per day, and the density of infected snails. This leads to a rate of increase in the total number of egg-laying schistosomes of $\alpha\sigma Y$, where σ is the human population density per unit accessible water area, Y is the current number of infected snails, and α, like β, is a constant depending on biological, social and environmental factors. Both α and β are proportional to the amount of water contact per day, though, in view of the different mechanisms involved, the appropriate measures of water contact for the two parameters may well be different. In particular, β is the typical target for measures of improved sanitation, whereas safe water supplies are directed at reducing α. However, the fact that providing safe water can also lead to a corresponding reduction in the contamination constant β by reducing the amount of time spent by the populace in the neighbourhood of snail colonies, may account for the observation of Scott and Barlow (1938) on the relative merits of the sanitation and safe water strategies.

The rates of flow of infection so far computed have to be set against the rates of loss of infection from the various possible causes. The number of egg-laying schistosomes may be reduced both by the mortality of the schistosomes and by that of their human hosts. However, current estimates of the lifetime of a schistosome suggest that the former should be much the more important factor, and it therefore seems reasonable to describe the total rate of loss of egg-laying schistosomes as γX, where X is, as before, the current number of egg-laying schistosomes, and γ is the per capita death rate of schistosomes, so that $1/\gamma$ is a measure of the typical life span of a schistosome. Note that there are a number of assumptions implicit in this description, of which perhaps the most tenuous is that the schistosomes have independent life spans, so that there are no crowding effects within a particular human host. At any level of parasitization which leads rapidly to the death of the human host, this is clearly not the case, but, as mentioned before, it still probably represents a good first approximation. In the snail host, the situation is quite the opposite, with cercarial release usually continuing until the death of the snail. This leads naturally to an expression δY for the overall death rate of infected snails, where δ is the per capita death rate of infected snails.

Finally, it is necessary to make some assumptions about the behaviour of the host populations. The human population can usually be reasonably supposed to be constant, since the time scale over which it changes is much longer than any of the time scales in the infection process. In contrast, snails have a relatively short life span, and the size of a colony rapidly reaches an equilibrium in which their vigorous breeding capability is balanced by the limitations of the available ecological resources. Thus, though for quite different reasons, it is also plausible to assume that the snail population has a constant size, N say, and therefore implicitly that the death of a snail is on

average balanced by the birth of another. The proportion q of infected snails is then given by $(N-Y)/N$. The sort of situation in which this assumption usually breaks down is one in which there is a substantial seasonal variation in the amount of water suitable for breeding, leading to dramatic changes in the snail population. Such variations may also change other parameters, in particular σ, the human population density per unit of accessible water area, but, as a first approximation, they are all taken to be constant.

The structure of the basic model, expressed in terms of the rates of increase and decrease of the numbers of infective units (here egg-laying schistosomes and infected snails) is now complete. The next stages in the argument would ideally be to estimate the various parameters in the model from field observations drawn from a number of communities (the parameters no doubt having different values in different areas, even when the strains of schistosome and snail are the same); to use these estimates to make predictions from the model of the effects on transmission of changing some of the parameters; and then to compare the predictions with the response actually obtained in the field. If satisfactory agreement, at least in qualitative terms, were obtained, the model could reasonably be used as a means of evaluating the likely effects of different control measures, as an aid to developing a strategy for control.

Unfortunately, few of the parameters in the model can be directly measured. The transmission parameters α and β, for instance, are particularly awkward to assess, and it is very difficult to imagine how to assign values to them from direct observation. Although efforts have been made to analyse some of their constituents, notably the water-contact rates estimated by Dalton and Pole (1978), the only satisfactory means of estimating them are indirect, and are based on the assumption that the model is, at least in part, a good one. It then becomes doubly important to check the validity of the model by testing its predictions against observation, since, with a minimum of four unknown parameters to play with, one can expect to find a reasonable fit to almost any set of data. It is possible that the forthcoming publications from the WHO project on Lake Volta may contain a sufficiently comprehensive body of data for such a quantitative exercise to be carried out. In the meantime, we shall attempt to examine the qualitative features of the model in the light of the less conclusive data at present available.

The first step in the analysis is to observe that when, as is usually the case where the disease is endemic, transmission is in equilibrium, the rates of increase and decrease in the numbers of each type of infective unit must balance. This gives two equations, the first from considering the egg-laying schistosomes and the second from considering infected snails:

$$\alpha\sigma\bar{Y} = \gamma\bar{X} \quad \text{and} \quad \beta\bar{q}\bar{X} = \delta\bar{Y} \tag{6.1}$$

where $\bar{X}$ and $\bar{Y}$ are the total numbers of egg-laying schistosomes and infected snails respectively in the community at equilibrium, and $\bar{q}$ denotes the equilibrium proportion of infected snails. The equations have two solutions: $\bar{X}$

and $\bar{Y}$ are either both zero, with the natural interpretation that there is no disease present, or both positive, corresponding to endemic transmission, in which case

$$(\alpha\beta\sigma/\gamma\delta)\bar{q} = 1$$

Note that, since $\bar{q}$ represents a proportion, and hence necessarily lies between zero and one, the latter possibility can only occur if

$$\alpha\beta\sigma/\gamma\delta > 1$$

The quantity $\alpha\beta\sigma/\gamma\delta$, which we shall denote by R, and which is usually referred to as the threshold parameter, is just the net (basic) reproductive rate of the parasite population under the ideal conditions when no snails are as yet infected; this last result merely states that the disease can be supported endemically if the parasite population, under uncrowded conditions, would tend to multiply, and not otherwise.

This simple statement, derived from quite elementary considerations, gives a clear indication of what is required if the disease is to be eradicated: R must be reduced to a value smaller than 1. Since R is just a product of the five parameters of the model, it is easy to deduce the qualitative effects upon it of various control measures. In particular, a given percentage reduction in any one of the parameters α, β and σ, or a corresponding increase in γ or δ, would have exactly the same effect on R. If also, as has been suggested, $\bar{q}$ is given in terms of $\bar{Y}$ as $1-(\bar{Y}/N)$, the endemic values $\bar{X}$ and $\bar{Y}$ can be expressed explicitly as:

$$\bar{X} = N\left(\frac{\alpha\sigma}{\gamma} - \frac{\delta}{\beta}\right) \quad \text{and} \quad \bar{Y} = N\left(1 - \frac{1}{R}\right) \tag{6.2}$$

it is interesting here to note that α, β, γ, δ and σ are no longer symmetrically represented in the total worm burden $\bar{X}$, so that a given percentage reduction in α, σ or $1/\gamma$, if not enough to reduce R below unity, is more effective in alleviating worm burden than a similar reduction in β or $1/\delta$.

The model also illustrates that it is possible to have no disease present, even when $R > 1$. In order to assess the relative likelihood of the two equilibria, it is necessary to consider the dynamics of infective units when the system is not in equilibrium. The net rates of change in their numbers are then no longer zero, but are given by the two differential equations:

$$\begin{aligned} dX/dt &= \alpha\sigma Y - \gamma X \\ dY/dt &= \beta X(1 - Y/N) - \delta Y \end{aligned} \tag{6.3}$$

of which Equation (6.1) are the special case when

$$dX/dt = dY/dt = 0$$

It is easy to analyse these equations, and to show that, if $R > 1$, the presence of any initial amount of infection ultimately leads to the endemic equilibrium. In

practical terms, if $R > 1$, there is a considerable danger that casually imported disease will sooner or later become established, even if the community is currently uninfected.

Of the various methods of control currently employed, sanitation is aimed at reducing β and safe water supplies at reducing α, though, as mentioned earlier, safe water supplies may also have an appreciable benefit through β as well. In either case, R is thereby reduced. A single round of chemotherapy would reduce the current level of X without changing R, hence the endemic equilibrium would in due course be re-attained. In order to impinge upon R, chemotherapy has to be repeated regularly, in which case it can be considered to act by increasing γ, thus reducing R.

The effect of applying molluscicide is more complicated. A reduced number N of snails clearly leads to a corresponding decline in the equilibrium worm burden, as given by Equations (6.2). On the other hand, R is not obviously affected, so that killing snails is apparently of little use as a means of eradicating the disease. Clearly, this cannot strictly be the case, since, if there are no suitable snail hosts, there can be no transmission. The resolution of the difficulty lies in the discussion preceding the emergence of β, where it was noted that β does depend implicitly on snail density. Since this is the only way in which R is influenced by the killing of snails, it would be of great interest to know more precisely what form the dependence takes. Broadly speaking, any density of snails sufficient to make it almost certain that a given miracidium has at least one snail within its radius of operation would give rise to essentially the same value of β, and hence of R. Consequently, reducing the number of snails in each colony by, say, a factor of 10 would have little or no effect on β if the average snail density were not brought down below one or two snails per miracidial search area. Thus molluscicide has to be directed at maintaining very low average snail densities, and, in view of the extremely resilient nature of snail populations, such an effort may often be rather difficult to achieve. In such cases, the killing of snails should probably be considered mainly as a means of alleviating worm burden, rather than as a potential aid in eradication.

There is a further problem associated with molluscicide, in that it kills many other organisms, as well as the snail hosts. A number of these organisms actively impede the miracidial stage of transmission, for instance by acting as decoys (Upatham and Sturrock, 1973). Since some of these species recover less quickly from the effects of molluscicide than do snail populations, there is a danger that miracidial efficiency could in some circumstances actually be improved as a result of molluscicide campaigns, with a consequent increase in R.

6.3 COMPARISON OF THE MODEL WITH DATA

The discussion at the end of the previous section shows how useful a simple mathematical model can be in making qualitative judgements about control

strategies. However, the value of such judgements depends on the model being a faithful representation of the transmission cycle, at least insofar as its broad outline is concerned. Unfortunately, there is one respect in which the current model is clearly deficient.

It has already been mentioned that most of the parameters of the model are difficult to estimate directly. However, if the model is valid, it immediately yields a means of estimating the value of R, the critical threshold parameter. This is because, at an endemic equilibrium, the proportion of uninfected snails $\bar{q}$ is equal to $1/R$, as follows from Equations (6.1). Now $\bar{q}$ is easily observed, and estimates, usually of $1-\bar{q}$, the proportion of infected snails, have been derived from field observations in many parts of the world: summaries of the findings are presented in Jordan and Webbe (1969), pp. 145–150, and in Anderson and May (1979b). Characteristically, the proportions of infected snails observed range from levels of the order of less than 1% in Egypt (*S. haematobium*) to around 7% in the Philippines (*S. japonicum*) and, in peak months, to 10% in Tanzania (*S. haematobium*), though much higher proportions were sometimes observed in individual colonies. The corresponding values for R are 1.01, 1.08 and 1.11, and it would require a proportion of infected snails of the order of 50% to reflect a value of R around 2.

This sort of figure may be compatible with an ideal mathematical system, but the transmission of schistosomiasis is hardly that. Many of the factors involved in transmission can be expected to vary widely from one community to another, and, over a period of time, within a particular community. It would be very surprising if they always changed collectively in such a way as to preserve R at a value within the narrow range 1.0 to 1.1, especially when 1.0 represents the lower limit of endemic transmission; the partial rather than total success of control measures strongly reinforces the feeling that R is not at all susceptible to being reduced below unity by a small push in the right direction. What, then, is the explanation for the apparent discrepancy between theory and observation?

The most obvious source of error lies in the detection of infection in the snails sampled in the field. There are two methods of detection principally in use: a snail is either kept under observation in the laboratory, to see if it is releasing cercariae, or crushed and examined under a microscope for evidence of infection, in the form of sporocysts. In either case, a snail infected less than about 3 weeks before sampling would appear to be uninfected, if, as would usually be the case, the snail was examined immediately upon being brought to the laboratory. However, as far as Macdonald's model is concerned, a snail should be counted as infected as soon as it is penetrated by a miracidium, since all subsequent miracidial penetrations are wasted. The distinction is important numerically, because the time taken for a snail infection to develop to the point where it is detectable is of a similar order of magnitude to the natural lifetime of the snail. An analysis of a model similar to the basic model, but allowing for the latent period of infection in the snail, shows that the basic model remains

valid, provided that an appropriate correction is made to allow for snails falsely recorded as uninfected. The precise correction for a sample drawn at random from the snail population, if only snails releasing cercariae are recorded as infected, is to multiply the proportion of snails observed to be infected by a factor of $1+[\delta(e^{l\delta'}-1)/\delta']$, where δ' is the death rate of uninfected snails and of snails with a latent infection, δ is the death rate of infected snails, and l is the length of the latent period (Barbour, 1978a; Anderson and May, 1979b).

The data given in Pesigan *et al.* (1958b), for *S. japonicum* in the Philippines, suggest the values $l = 9$ weeks, $1/\delta' = 16$ weeks, $1/\delta = 6$ weeks, which would lead to a correction factor of around 3.0. However, their method of sampling snails was known to be age-specific, and allowance for this reduces the correction factor to around 2.0. Furthermore, they used a crushing technique to examine for infection, which probably meant that a significant proportion of the latently infected snails were in fact detected and included in their estimates, with the result that the correction factor should probably have been further reduced. Even without this, applying a correction factor of 2.0 to their data on the proportions of infected snails gives an effective proportion of around 14%, which is still much too small to give a reasonable value for R.

Anderson and May (1979b) also discussed the effect of the latent period, in the light of a wide selection of data gathered from the literature. The example they chose to examine in numerical detail was that of *S. mansoni* in St. Lucia. Starting from the findings of Sturrock and Webbe (1971), who estimated $l = 5$ weeks, $1/\delta' = 6.6$ weeks and $1/\delta = 1.6$ weeks, and who observed proportions of infected snails close to 5%, they computed a correction factor of 5.5. Since Sturrock and Webbe tested for infection in snails by looking for cercarial release, and returned uninfected snails within 30 h of capture, they included no latent infections in their figures. However, their method of sampling snails was significantly age-specific, and a detailed analysis shows that, even allowing for latent infections, their data indicate that only 13% of snails were infected. It might conversely be argued that miracidia can reasonably be expected to be age-specific in their choice of host, but the age–prevalence curves of Sturrock and Webbe show no evidence of this. Other data relating to *S. mansoni* in St. Lucia give values $1/\delta' = 3.6$ weeks and $1/\delta = 2.7$ weeks (Sturrock, 1973), and proportions of infected snails of between 1% and 1.5% (Sturrock, 1973; Jordan, 1977), all of which would suggest even smaller corrections. Once again, the corresponding values of R are much too small. The above remarks also illustrate the need for a very careful determination of snail infection rates; the above considerations would be unnecessary if the snail samples were observed over a period long enough for latent infections to mature, and if those dying in the interim were crushed and examined.

The next most obvious candidate for explaining the unacceptably low values of R derived from the observed proportions of infected snails is heterogeneity: geographical, temporal, behavioural, or even among snails. Substantial

geographical and temporal heterogeneity is clearly in evidence in almost every study of snail infection rates, with Webbe (1962), for example, recording overall proportions of infected snails of below 3% for 14 months, of between 5% and 8% for 4 months, and of 12% for 2 months, but with individual colonies frequently yielding samples of 200 or more snails of which more than 50% were infected. It is also clear that a straight average of all the data recorded (number of infected snails/total number of snails) does not give an appropriate overall estimate. To take an absurd example to illustrate the point, it is obviously not right to include in the estimate any snails sampled from an area totally inaccessible to the native population. However, the fact that any such area must necessarily, in the absence of other host species, be free of infection points to the fact that it may be possible to compute an estimate of the overall effective proportion of infected snails, and hence of the parameter R, by using a suitably weighted average of the data, with weights deduced from observable quantities such as the local proportion of infected snails.

This is essentially the approach taken in Barbour (1978a). A model incorporating geographical and social heterogeneity is developed from the basic model, by making allowance for the varying intensities with which different hosts visit different water-contact sites. Its qualitative behaviour is broadly that of the basic model, though the exact representation of the threshold parameter R is now more complicated. Whilst it is no longer possible in general to estimate R exactly without first knowing the water-contact intensities, upper and lower bounds for R can be derived in terms of the observed values at the different water-contact sites of three measurable quantities: the snail density ρ, the proportion p of infected snails, and the accessible water area A. For instance, if L different sites are sampled, yielding the values ρ_j, p_j and A_j, $1 \leqslant j \leqslant L$, then a lower bound for R is given by:

$$[\sum_{j=1}^{L} p_j^2 \rho_j^2 A_j/(1-p_j)^2]/[\sum_{j=1}^{L} p_j^2 \rho_j^2 A_j/(1-p_j)]$$

and an upper bound by:

$$\max_{1 \leqslant j \leqslant L} 1/(1-p_j)$$

Similar formulae hold when ρ, p and A vary spatially in a continuous rather than a discrete manner.

The most important qualitative conclusion to be derived from the estimates is that assuming a homogeneous environment always leads to an underestimate of R. A similar phenomenon was also noted in connection with the spread of influenza by McNamee (1978). It occurs here essentially because of the way in which increased water contact leads to an increase in both channels of infection, and hence has a non-linear effect on transmission. When actual data are considered, the effect can be dramatic. For instance, in Barbour (1978a), data from Pesigan *et al.* (1958b) were used to estimate R for the community around Malirong, the correction factor of 2.0 mentioned above being applied to the snail infection rates, to allow for under-recording of infected snails. If a direct average over time and space were used to assess the (corrected) proportion of infected snails, the value of R obtained would be about 1.1. However, the bounds above, used in conjunction with an analogous formula to allow for the substantial seasonal variation encountered, give a value for R of around 4.0.

A very noticeable feature of the results is that the upper and lower bounds for R, in both dry and rainy seasons, are very close together, indicating that transmission in Malirong was extremely focal in character, and that the relatively short season of high transmission was very much the most important part of the cycle. Indeed, if the data for May–June 1954 in Table XLVII of Pesigan *et al.* (1958b) were representative of dry-season transmission, and that for February–March 1956 of the wet season, the cycle would be broken if no transmission were allowed to take place at Malirong River Pocket No. 2 during the wet season. The proportion of infected snails observed there (39% actual, 78% corrected) overwhelmingly dominates the computation of the threshold parameter. The estimate of the threshold parameter is therefore very sensitive to this one particular measurement; if the actual proportion of infected snails observed there were read as 30% instead of 39%, an error apparently made during the calculations in Barbour (1978a), the estimate of the threshold parameter would be reduced to 2.0.

Since the figure of 39% is exceptional in Table XLVII of Pesigan *et al.* (1958b), it is natural to try instead the figures for March–April 1955 as representative of the rainy season. If this is done, the (corrected) value of the threshold parameter is found to lie between 1.82 and 2.02, transmission now being almost entirely dependent on two sites, Malirong River Pocket No. 2 and Villaco Creek, during the wet season. This once again suggests that an energetic campaign for a limited period each year at just one or two sites would be enough to eliminate transmission. However, a value of R of around 2 still seems rather too small to account for the observed stability of transmission, and the high dependence on one or two sites and times seems much too good to be true. The focal dependence is in part related to an assumption in the model that an increase in water contact has a proportionate effect on both α and β, which is perhaps more appropriate to *S. haematobium* than to *S. japonicum*. But any more uniform average reduces the estimate of R, further detracting from the plausibility of the model. In summary, the qualitative findings, that it is important to concentrate attention on sites and times at which $p_j \rho_j$ is large, are useful, at least to the extent that Macdonald's model is valid; but, from the data in Pesigan *et al.* (1958b), stability of transmission, expressed by a reasonably large value of R, can only exceptionally be attained, and then only at the expense of accepting that transmission is highly vulnerable to a very limited eradication campaign. The clear implication is that the model does not give an adequate representation of reality.

There remains the possibility of heterogeneity within snail populations.

Anderson (1978) shows how a number of laboratory studies in the literature, concerned with the penetration of snails by miracidia, give indirect evidence that some snails are more prone to penetration than others. Further indirect evidence of this comes from the shape of the age–prevalence curves for the infection of snails, as for instance in Sturrock and Webbe (1971), in that prevalence begins to decline in the older age groups (Fig. 6.3). Should this indeed be the case in the field, it would have implications for estimating the proportion of infected snails relevant to Macdonald's model. For instance, if a certain part of the snail population were completely resistant to miracidia, it should not be treated as if part of the population of potential snail hosts. This in turn would imply that the estimates of R should be increased. However, a number of authors argue against heterogeneity being significant in the field, and the decline in prevalence observed by Sturrock and Webbe is very slight. In view of this, it is very unlikely that the effect would be large enough to resolve the difficulties described above.

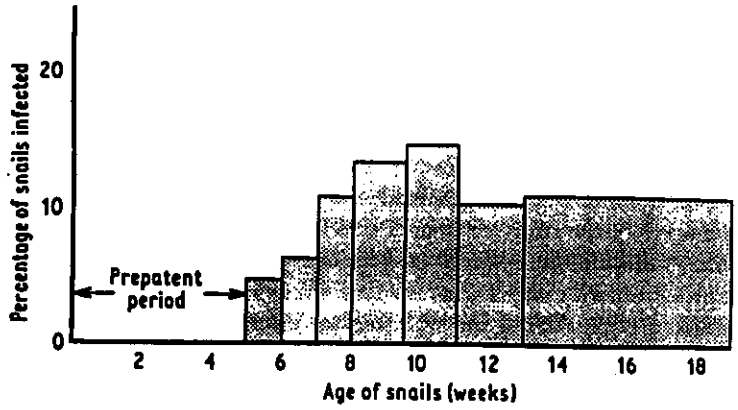

Figure 6.3 An example of an age–prevalence curve of schistosome infection in a snail population. The prevalence of *Schistosoma mansoni* infections in a population of *Biomphalaria glabrata* from a site in St. Lucia in 1970 (data from Sturrock and Webbe, 1971.)

Since it has proved awkward to reconcile the data of Pesigan *et.al.* (1958a, b) with the models discussed so far, it is appropriate to mention that an important feature of *S. japonicum*, not explicitly accounted for in the model, is that it is also harboured in a number of animal hosts. Hairston (1961) was interested in assessing the parts played by the various hosts, and reached the conclusion that, whereas human beings made the most important contribution to transmission in Malirong, rats might not be far behind, and suggested rat control might be better than snail control. Curiously enough, Pesigan *et al.* (1958a), arguing from the same data, deemed rats to be of little importance, and were much more concerned about dogs and cows. More recent models taking animal reservoirs into account include that of Lewis (1975b). In actual fact, the model of Barbour (1978a) discussed above, by making allowance for varying behaviour among definitive hosts, implicitly includes any animal hosts, so that no further changes are required. There is a slight objection to this, since the death rate of small animal hosts such as rats can be much greater than that of the schistosome, and this fact leads to a slightly different model. Nonetheless the presence of animal hosts cannot resolve the fundamental problem, which is that Macdonald's model requires much higher snail infection rates than are observed in practice.

6.4 IMMUNITY IN THE HUMAN HOST

With the stability of a model based on Macdonald's assumptions somewhat in doubt, it is natural to consider what other possibilities there are. In view of the discussion in Section 6.1, the only real alternative is one based on control exercised through the human, rather than the snail, host. The most likely form that this would take would be through some form of acquired immunity.

Evidence for acquired immunity comes mainly from two sources, experiments with animals and age–prevalence curves (see, for example, the discussions in Smithers and Terry, 1969 and in Warren, 1973). Immunity has been demonstrated in the laboratory in experiments on monkeys, baboons, rats and mice. It is thought to be stimulated by the presence of adult worms in the host, and is most effective in protecting against further infection rather than in destroying the worms which initiated the response (concomitant immunity). However, the detailed mechanism by which this is accomplished is obscure (Cohen and Sadun, 1976), and is probably different in different hosts, as, too, is the degree of concomitant immunity induced. There have been few experiments involving human beings, and no good evidence of the existence of immunity in man can be drawn from them.

The situation is apparently clearer as regards age–prevalence curves. It is almost always found that the prevalence of infection within the different age groups in a community follows a characteristic pattern, increasing to a peak around the early teens, and then declining to a lower level, which remains more or less constant beyond the age of 30 (Fig. 6.4). A similar pattern is obtained if egg output is plotted against age. Such curves are readily interpreted in terms of partial or total immunity to further infection conferred for a time by a certain degree of exposure. Bradley and McCullough (1973), in particular, were able to demonstrate that a model incorporating acquired immunity gave a good explanation of some data on *S. haematobium* drawn from a community in Tanzania. Unfortunately, studies also show that water contact varies with age in a broadly similar way. Since this could also give rise to the observed age–prevalence curves, it cannot necessarily be concluded that their

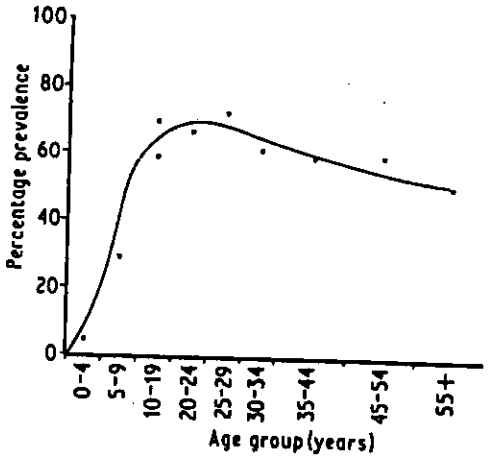

Figure 6.4 An example of an age–prevalence curve of schistosome infection in a human community; the prevalence of *Schistosoma japonicum* in various age groups of a human community at Palo in the Philippines (data from Pesigan *et al.*, 1958). Solid points, observed values; solid line, curve fitted by eye.

characteristic shape is evidence of acquired immunity. Indeed, in the recent paper by Dalton and Pole (1978), with data on *S. haematobium* in Ghana, the authors concluded that 'age was less important than degree of exposure as a contributory factor to variations in infection rates'. On the other hand, the evidence of Kloetzel and da Silva (1967) (*S. mansoni* in Brazil) shows that the characteristic curves are obtained in populations of adults, following their arrival as immigrants in an endemic area, if 'age' is measured starting from their arrival in the area. This observation represents the most direct evidence to date that a controlling mechanism is at work in the human host.

Just as with the earlier models based on snail moderation, there are many possible ways in which to go about specifying a model incorporating human immunity. As before, we shall begin by erring on the side of simplicity, and then see what sort of modification may be necessary to account for the available data. The first step is to note that it is now important, even at the most basic level, to distinguish individual human hosts, rather than aggregate all the schistosomes in the population, since it is the effect of schistosomes upon the individual hosts which is supposed to exert the moderating influence on the transmission cycle. One way of doing this is to keep track of the numbers of human hosts having various levels of infection – this is in fact the way that snails were treated previously, with just one level of infection being distinguished – and to use these as the basic variables in the equations. In a sweeping attempt at simplification, we shall take this approach, and consider only three classes of human host: those that are currently susceptible (Z_0) those that are infected (Z_1), and those that are immune (Z_2) – see also Lewis (1975a). Since only one level of infection is allowed for, the model effectively assumes

that currently infected persons are immune to further infection. A period of infection in a host ends when the schistosomes he carries have all died, and it is followed by a further time during which he remains immune from re-infection, after which he becomes susceptible once again. No account is taken of human host mortality, with slightly less than the usual justification, since the average period of infection might be appreciably longer than the average lifetime of an individual schistosome pair, and may therefore be more comparable with a human lifetime, but this loss of realism is likely to be less than that implicit in some of the other assumptions. The snail host is treated as before, so that Macdonald's mechanism of snail moderation is retained, but now only infected humans contribute to the snail infection rate.

Much as with the basic model, suitable postulates are made about the rates of flow of infection. The rate at which susceptible human hosts are infected is taken to be $aY(Z_0/A)$, where Y is the current number of infected snails, A is the accessible water area – Z_0/A thus replacing the constant σ previously used – and a is a constant analogous to, but not quite the same as, α. Individual infections are assumed to terminate at a rate g (to be compared with γ), so that there is an overall flow at rate gZ_1 between the infectious and immune classes. For similar reasons, there is a flow at rate cZ_2 between the immune and susceptible classes, where $1/c$ represents the average length of time that immunity subsists after infection has terminated. Finally, the rate of increase of infected snails is $bZ_1(1-Y/N)$, where b is analogous to β, and it is compensated by a loss of infected snails through death at an overall rate δY.

These rates give rise to the following equations for the four populations:

$$\begin{aligned} dZ_1/dt &= aYZ_0/A - gZ_1, \quad & dZ_2/dt &= gZ_1 - cZ_2 \\ dZ_0/dt &= cZ_2 - aYZ_0/A, \quad & dY/dt &= bZ_1(1-Y/N) - \delta Y \end{aligned} \tag{6.4}$$

The total human population $Z_1 + Z_2 + Z_0 = M$ is constant. The complete absence of infection, represented by $Z_0 = M$, $Z_1 = Z_2 = Y = 0$, is always an equilibrium of the equations, and is stable only if $R' = ab\sigma/g\delta \leqslant 1$ (compare with R). If $R' > 1$, there is another equilibrium, corresponding to endemic infection, at which, in particular, the proportions of infected human and snail hosts are given by:

$$\begin{aligned} Z_1/M &= \frac{(1-1/R')}{k(1+g/k\rho a)} \\ Y/N &= \frac{(1-1/R')}{(1+k\rho\delta/b\sigma)} \end{aligned} \tag{6.5}$$

where $\rho = N/A$ is the snail density, and $k = 1 + g/c$. It is a stable equilibrium, and the solution to Equations (6.4) following any introduction of infection is eventually attracted to it. Thus the situation, as regards permanent eradication, is superficially very similar to that discussed in Section 6.2: R' has to be reduced

below unity, and the factors influencing R' are very much those that influence R.

Estimating R' from field observations is rather more difficult than was the case for R, since it is no longer directly related to the easily observable quantities Z_1/M and $\bar{Y}/N$. There is, however, an analogous formula:

$$R' = 1/[(1-\bar{Y}/N)(1-kZ_1/M)]$$

showing that an estimate of R' derived from observations of endemic transmission would now involve the proportion of infected hosts, as well as of infected snails. The factor $k = 1+g/c$ can in principle be estimated. For instance, if longitudinal studies of the population were available, $1/g$, the mean length of an infected period, and $a\bar{Y}/A$, the rate of incidence of the disease among susceptibles, could be directly estimated. Then the equilibrium equation:

$$Z_1/M = (1/g)/\left(\frac{1}{g}+\frac{1}{c}+\frac{A}{a\bar{Y}}\right)$$

could be used to derive an estimate of c, and hence, combining it with the estimate of g, an estimate of k would be obtained.

Taking Bradley and McCullough's (1973) data for *S. haematobium* in Tanzania, and analysing their age–prevalence curves as indicated in the following section, one derives estimates $Z_1/M = 0.5$, $a\bar{Y}/A = 0.2$ per year and $1/g = 10$ years, leading to values of 5 years for $1/c$ and 4 for $1/(1-kZ_1/M)$. Incorporating the value of 0.38 for the proportion of infected snails, derived from the Tanzania data of Sturrock and Webbe (1971) by allowing for the effects of snail latency and of the age structure of their snail sample, would then give an estimate of R' of around 6.5, whereas, if Webbe's (1962) proportion were used; R' would be evaluated at around 4.5. These estimates are based on assuming that the whole population is behaving as if over 37 years of age, which is the age at which Bradley and McCullough observed that it had apparently reached equilibrium with respect to the infection. The much greater prevalence and intensity of infection in the younger age groups indicate that the true value of threshold is probably considerably larger.

The age–prevalence curves for *S. japonicum* in Malirong, as recorded in Pesigan *et al.* (1958a), suggest the estimates $Z_1/M = 0.7$ and $a\bar{Y}/A = 0.14$, which, for any value of $1/g$ less than 17 years, would suggest that $1/c = 0$, or, equivalently, that immunity to further infection lasts no longer than the current infection. Under these circumstances, $k = 1$, and $R' = 3.3/(1-\bar{Y}/N)$, or between 3.5 and 6.0, depending on which of the estimates of the previous section is taken for $\bar{Y}/N$. However, the shape of the age–prevalence curve, which shows a small decline from its peak at around age 20, suggests that $1/c$ may in fact be positive, even if rather small when compared with $1/g$. A further interesting piece of evidence is the pattern of response to an intradermal antigen test also carried out at Malirong, which gave higher rates of prevalence than stool examination. If the steady-state proportions registered by this test

were assumed, as is tempting, to be measuring $(Z_1+Z_2)/M$, a direct estimate of k would be obtained, since:

$$[(Z_1+Z_2)/M]/[Z_1/M] = k$$

This would suggest a value of 25/21 for k at Malirong, giving the estimates $R' = 6/(1-\bar{Y}/N)$ or between 6.5 and 12, $1/c = 6$ years and $1/g = 30$ years. Even though 20–30 years seems much too long a time for a single infection to last, it is encouraging to see that the estimates of R' are very much larger than those previously obtained for R. The explanation for the long periods of infection may be that, in practice, concomitant immunity is not total, and that the period of infection is effectively lengthened by intermittent reinfection. Clearly, a more sophisticated model would be needed to properly describe this.

It should be noted that, whereas the incidence rate $a\bar{Y}/A$ was estimated as 0.14 per year from the age–prevalence curves in Pesigan *et al.* (1958a), the same study also included direct measurements of the rate of incidence in children. Between the ages of 5 and 10, the rate of incidence was apparently between 45% and 50% per year. Such a rate appears to be quite incompatible with their age–prevalence curves.

Equations (6.5) can be used to predict the qualitative effects of modifying the parameters of the model by amounts insufficient to reduce R' below 1. Any reduction in R' reduces Z_1/M through the factor $1-1/R'$, which, however, is relatively insensitive to changes in R' if R' is at all large. For instance, reducing R' from 12 to 6 would only reduce $1-1/R'$ by around 10%. The parameters which influence Z_1/M other than through $1-1/R'$ are g, ρ, a and c. If $g/k\rho a$ is much larger than one, Z_1/M is reduced more or less in proportion to reductions in ρ, a and $1/g$, and is insensitive to changes in c. In this case, the dependence of Z_1 on the parameters is essentially the same as that of X in the basic model. If, at the other extreme, $g/k\rho a$ is much smaller than one, Z_1/M is insensitive to ρ and a, and is approximately inversely proportional to $k = 1+g/c$, k itself being insensitive to changes in g and c if g/c is much smaller than one. Thus, of all the parameters, the prevalence Z_1/M is most consistently sensitive to changes in g.

If the lack of uninfected snails exerted no moderating influence at all upon the transmission cycle, the equilibrium value of Z_1/M would be $(1-1/R')/k$, and so a small value of $g/k\rho a$ shows that human immunity is effective in controlling transmission. Similar consideration of the value of $\bar{Y}/N$ shows that moderation through the snail host is effective if $k\rho\delta/b\sigma$ is small. The quantities $g/k\rho a$ and $k\rho\delta/b\sigma$ are linked by the fact that their product is equal to $1/R'$, giving some feeling for the relative importance of the two mechanisms in controlling transmission. Now it follows from Equations (6.4) that, at equilibrium:

$$\frac{\bar{Y}}{N}\left(\frac{M}{kZ_1}-1\right) = g/k\rho a \quad \text{and} \quad \frac{kZ_1}{M}\left(\frac{N}{\bar{Y}}-1\right) = k\rho\delta/b\sigma$$

enabling one to estimate $g/k\rho a$ and $k\rho\delta/b\sigma$ in terms of $\bar{Y}/N$, Z_1/M and k. It is

interesting to note that, on the above figures for Malirong, $g/k\rho a$ is estimated to lie between 0.1 and 0.2 and $k\rho\delta/b\sigma$ between 0.65 and 0.85, if the value of 0.5 from Section 6.3 is taken for $\bar{Y}/N$, and the grand average estimate of 0.1 for $\bar{Y}/N$ would yield values of the order of 1/35 and 8 respectively. In other words, the level of transmission is apparently limited mostly by the effects of immunity in the human host. Since also g/c is estimated to lie between 0 and 0.2, the situation is precisely the one in which, for a given value of R', the prevalence $\bar{Z}_1/M$ is least sensitive to changes in the parameters of the model. The corresponding estimates of $g/k\rho a$ and $k\rho\delta/b\sigma$ for *S. haematobium* in Tanzania are 0.13 and 1.22, if Sturrock and Webbe's snail infection rate is used, and 0.02 and 14 if Webbe's is taken, with g/c around 0.5; in either case, human immunity appears to be much the more important.

There are two main drawbacks to estimates such as these. The first is the tentative nature of the model on which they are based. It would require a certain stretch of the imagination to discount the possibility of superinfection in the human host. It would require a rather larger effort to believe that the human population was immortal, and had reached equilibrium with the infection to the extent that age–prevalence curves were effectively flat. Finally, the discussion in Section 6.3 shows the dangers of supposing that the host population and its environment are to any degree homogeneous. Despite all these criticisms, it would be surprising if the qualitative picture were different from that outlined here, even if the quantitative estimates were considerably altered.

The second drawback lies in making estimates on the basis of the curves of age against prevalence and egg output. The simple model is, as it stands, too rough and ready to make good predictions of the shape of the age–prevalence curves, with the result that it is difficult to know quite how estimates from the curves should be translated into the terms of the simple model – just as, to allow for field data, Macdonald's model had to be variously adapted. The method adopted here, as already remarked, is likely to underestimate the true value of R. Then, as has widely been observed, prevalence ought naturally to be related to degree of exposure, and age–prevalence curves can therefore be expected, at least in part, to derive their shape from the way that exposure varies with age. Thus, for instance, the equilibrium prevalence $\bar{Z}_1/M$ was estimated by referring to the almost steady prevalence achieved in later life, whereas the rate of incidence $a\bar{Y}/A$ among susceptibles was estimated from the earlier part of the curve. Since exposure is often found to decline in later life, an inconsistency in the estimates may be being introduced by supposing a constant level of water contact. The same considerations also apply if $1/g$ is estimated by assuming that the age–prevalence curve declines from its peak because of loss of infection due to immunity.

However, with regard to the argument that the shape of the age–prevalence curve is a consequence only of variations in the amount of water contact with age, and that immunity is unimportant, there is more to be said. The evidence

of Kloetzel and da Silva (1967) has already been mentioned. It is supplemented by that of Bradley and McCullough (1973), who, whilst observing a very decided pattern of variation in both prevalence and egg output over the first 20 years of life, were unable to detect any marked change in water-contact rates during this period. To explain their age–prevalence curves in terms of varying exposure alone would require a reduction in exposure of at least half between early and late childhood. However, there is a further, more serious problem: variable patterns of exposure do not in themselves exert any controlling influence on the transmission cycle. Thus, if immunity were not an effect significant enough to show up on age–prevalence curves, one would essentially be back to Macdonald's model, and all the problems of its lack of stability that are removed by admitting an immunological response. It might be possible to argue for some other mechanism of moderation through the human host, but any other explanation which accounted for the age–prevalence and egg output data in Bradley and McCullough (1973) would seem to have to be rather contrived. It therefore seems very likely that acquired immunity in the human host is the most important natural factor in limiting the transmission of schistosomiasis.

It has been noted earlier that, under these circumstances, the level of infection in the human population is relatively insensitive to variations in the transmission parameters, but may be somewhat more responsive to variations in $1/g$, the average duration of an infectious period, this advantage, however, being minimal if $1/g \gg 1/c$, where $1/c$ is the mean duration of immunity beyond the end of an infectious period. The most natural way of reducing $1/g$ is by regular screening and chemotherapy. However, in applying such a policy, the development of residual immunity might be impeded, and $1/c$ reduced as well, thus eliminating the extra sensitivity that could have been hoped for. In any case, the evidence of the data considered above suggests that $1/c$ is likely in practice to be smaller than $1/g$, and one must probably accept that evolution has succeeded in finding the most stable arrangements for transmission that were available to it.

6.5 STOCHASTIC MODELS

In the previous sections, not much has been done to incorporate into the models any element reflecting the part that chance plays in transmission. The treatment of events with random outcomes has so far been to decide on an 'average outcome', and to suppose that it always occurs. For example, a miracidium, which may or may not succeed in infecting a hitherto uninfected snail, is taken always to have infected a certain small fraction of a snail. Yet it is clear that, in reality, transmission depends upon the outcome of a succession of random events, and it is logical to try to assess the extent to which this is important

Macdonald (1965), in his pioneering work, was very concerned with the effects of randomness, for the following reason. Adult schistosomes, being dioecious, cannot reproduce unless they mate. Hence they must share a human host with at least one schistosome of the opposite sex, making the distribution of male and female schistosomes among the human population important when calculating egg output. In order to discover what this distribution might be, it is necessary to build a stochastic model. Macdonald supposed that the cercariae of each sex made successful penetrations individually and at random, with no preference for any particular host. These assumptions give rise to a specified distribution of adult schistosomes among hosts for any given overall level of parasitization, and, in particular, imply that, to a good approximation, each host carries independent numbers of male and female schistosomes, each distributed according to a Poisson distribution. If one supposes also that, within a given human host, schistosomes pair off if they possibly can, one can deduce the average egg output for each overall level of parasitization.

This was as far as Macdonald took his stochastic argument. He incorporated the average egg output, as a function of overall worm burden, into a model similar to that described in Section 6.2, and thereafter argued deterministically. But the contribution of the random model was important, because it raised an interesting possibility. Suppose that $2m$ schistosomes, which may be of either sex, are distributed at random among a population of M human hosts, as implied by Macdonald's model. Then, if $m \ll M$, the chance of a given female schistosome being mated is of the order of m/M, and hence the overall reproductive rate of the parasite population is, on average, proportional to m^2/M. On the other hand, the overall death rate of parasites is proportional to m. Comparing these two expressions, it follows that the ratio of reproductive rate to death rate is proportional to m, and hence that, if m is reduced far enough, the parasite population may fail to reproduce itself, and ultimately die out. Put another way, the net reproductive rate of schistosomes is proportional to the chance that a female schistosome is mated, and this chance declines as m/M is reduced. The critical value of m, below which the population is no longer viable, is called the breakpoint (see Chapter 2).

The above formulation has to be examined in the light of observation. The main conflict with experimental evidence is that, in most parasitic diseases, the distribution of parasites among hosts is not usually found to follow the Poisson distribution. Instead, it is usually the case that most parasites are aggregated among a few very heavily infected hosts, the rest being lightly infected or uninfected. Such a pattern was observed by Bradley and McCullough (1973) in egg output from human schistosomiasis. In May (1977b), the effect of a range of different distributions on Macdonald's model was explored. The most important conclusion to be drawn was that, if aggregation is sufficiently intense, there may be no breakpoint, because the chance of a given female being mated may not be reduced to zero by reducing m. Since there are quite plausible mechanisms for transmission which would lead to high aggregation (Barbour, 1978b), the significance of Macdonald's breakpoint remains in doubt.

These models, though based on certain stochastic arguments, are still treated deterministically when the whole transmission cycle is considered, and are therefore little different in this respect from the earlier models. However, Nåsell and Hirsch (1973) went further, building a model in which the transmission mechanism explicitly included the randomness of events, and whose solution yielded a probability distribution for the level of infection and its distribution among the hosts. This was an important advance upon the previous models, and led, directly or indirectly, to much of the subsequent interest in theoretical models for schistosomiasis. Their model is more difficult to analyse than Macdonald's, as is to be expected with a stochastic formulation, but gives broadly the same picture, thereby lending some justification to the policy of approximating the stochastic by the deterministic. However, it too is not really a stochastic model, since, in order to facilitate the analysis, a number of random events were again replaced by 'average outcomes'. Unfortunately, predictions of quantities of an essentially random nature are inclined to be very sensitive to this sort of approximation, and so the stochastic information, which might have been expected from it as a supplement to Macdonald's findings, has to be treated with caution. In particular, their model predicts a Poisson distribution of parasites among hosts, and is unable to give any extra information on what is perhaps the most interesting question of a genuinely stochastic nature: in a community in which there is currently no infection, but where infection could potentially become established, what is the chance of an imported infection taking hold?

This question was addressed by Lewis (1976), and also in Barbour (1978b), where a simple fully stochastic model was proposed based on Macdonald's assumption of moderation via the snail host. As before, analysis of the stochastic model confirmed the view that a deterministic model gives an adequate description of endemic transmission. A formula for the chance of an imported infection becoming established was also derived, and it was shown that, in order to protect against such a possibility in an uninfected locality, the parameters β and γ of the model in Section 6.2 – in practice, improved sanitation, and screening and treatment of immigrants – appeared to give the best response for a given percentage change. However, information relating to genuinely stochastic effects still appeared to be much more vulnerable to perturbations in the model than was the information derived from the deterministic models, and so the results of simplified models ought perhaps to be treated with circumspection.

Constructing more realistic stochastic models requires much finer detail than that required for a deterministic model. This is principally because, in a deterministic model, it is enough to specify rates of flow, whereas, in a stochastic model, more information is required about how the flow takes place. As an illustration of the extra effort that is entailed, as well as of the greater

insight that can be obtained, we shall conclude the section with a deeper analysis of the flow of infection between snail and man, using the data of Bradley and McCullough (1973) to provide the evidence on which to base our model.

In the models of the earlier sections, an expression was derived for the average rate of flow of infection into the human host population. However, many different random mechanisms could lead to the same average rate of flow. Both Hairston and Macdonald assumed, as is natural, that a human host was subject to regular invasions by individual cercariae, arriving according to a Poisson process. This assumption implies that the proportion of uninfected hosts should decline exponentially during childhood except for an initially slower phase which comes about because cercariae of both sexes are needed to cause overt infection. Bradley and McCullough's data confirm an exponential decline over time in the proportion of uninfected hosts, with about 20% succumbing each year, but apparently without the deviation predicted by Macdonald's analysis. This leads to the question: why is it that, despite constant exposure to hazardous water, children do not become infected more rapidly than is observed? It could be the case that the pattern of incidence merely reflects the times at which children first start to expose themselves to infection, or has to do with differential susceptibility, but it would be difficult from such hypotheses to account for the observed age–prevalence curves. It seems more likely that, as suggested by Warren (1973), the low rate of infection is the result of low cercarial densities, conditions less ideal for infection than those found in the laboratory, and some form of defence in the human host against minor challenge infections; this is the explanation that we shall accept hereafter.

On this hypothesis, the data of Bradley and McCullough actually imply a mechanism very different from Macdonald's. They record peak egg output at around age 9, and peak prevalence some 4 or 5 years later, which, with an incidence of 20% per year, would mean that, at the most important ages for transmission, the schistosomes harboured by a human host would on average have been delivered at only two successful infections. This suggests that cercarial penetrations do not necessarily occur singly, but in groups, as envisaged in some of Tallis and Leyton's (1969) models, and that the aggregated distribution among hosts indicated by egg output data can be explained, at least in part, by the random distribution of the numbers of cercariae in each infecting group. Of course differing amounts of water contact may also have their effect, as may differences in the efficiency of defensive mechanisms in the human host.

Group infection would also have other consequences. It may keep the chance of a female schistosome being mated large enough (even at low infection rates) to make the existence of a breakpoint unlikely and the precise degree of aggregation qualitatively unimportant. It would also render the detail of the mating mechanism less important, since it is likely to be enough to suppose that pairs are only formed from among a single infecting group. This is

because schistosomes are thought unlikely to be able to survive unmated for more than a few months, whereas the above data indicate an average period of five years between infections.

In view of these considerations, the following modification of the infection process in the model described in Section 6.4 is proposed, to account for Bradley and McCullough's data on *S. haematobium* in Tanzania. Each human host is assumed, as before, to be susceptible, from around the age of 1, to infection by groups of cercariae arriving as a Poisson process of rate $a\bar{Y}/A$, the numbers of worm pairs successfully delivered at each infection being independent and identically distributed. However, after receiving two such infections, a human host becomes immune to further infection until all the worm pairs that he has so far acquired have died. The subsequent pattern of infection is then taken to be similar to that of the model of Section 6.4, with each single infection again conferring immunity and with susceptibility between periods of infection being reduced relative to that during childhood, in that the rate of incidence is lower and the number of worms acquired at an infection is smaller. The model gives a very good fit to both the prevalence and the egg output curves of Bradley and McCullough, if 1. the initial rate of incidence is taken to be 0.2 per year, 2. the productive lifetime of a worm pair to be 7.5 years, 3. the duration of infection resulting from either of the first two large groups of worm pairs to be 13–15 years, and 4. that from any subsequent invasion to be 10 years, 5. the final rate of incidence to be 0.1 per year and 6. the ratio of the sizes of the larger initial and smaller subsequent groups of worm pairs to be 4.5:1. The duration of infection resulting from a group of worm pairs arriving simultaneously is likely to be longer than that of a single pair, because the productive lifetime of a worm pair is not a fixed quantity, and because overt infection lasts until the last pair ceases laying. Rather curiously, Bradley and McCullough's data suggest that the productive life of a worm pair may span a relatively definite length of time, in that the coefficient of variation is smaller than that of, say, an exponential distribution. Naturally enough, the duration of an infectious period seems rather more variable. The figures for worm lifetimes are also rather larger than those usually quoted in the literature, though Bradley and McCullough themselves suggested a similar value.

It can, of course, quite reasonably be argued that, with a model as complicated and as tailored to a particular set of data as this, it is hardly surprising that a reasonable fit is obtained, and that there may be many other models of equal complexity which would explain the data equally well. Variation in water contact has already been discussed, and the reasons against its being the only explanation for the age–prevalence curves have been clearly explained; but it may well contribute in part to the peaks of intensity and prevalence, making the above estimates less reliable. Bradley and McCullough themselves favoured an immunity which took several years to develop. Although superficially similar to the above formulation, it differs in one important respect: it would not exercise any moderating influence on

transmission through children of less than ten years of age, whatever the intensity of transmission. This means that if, as seems plausible in view of their egg output, children under ten could alone maintain transmission in Mwanza, the transmission intensity must be being limited by the lack of uninfected snails, and one is again returned to the problems of Section 6.3. However, time could still, with exposure, be a contributory element in the development of immunity. And there may be other possibilities. But it is interesting that it is much more difficult than one might suppose to concoct a satisfactory model for the mechanism of infection.

The curves relating egg output to age, to which the model has been fitted, are based on the sample averages of the egg counts of the members of each age group. However, the variability of the counts between one person and another is very striking, and average values only give a poor picture of the real situation. May (1977b) considered the effect on Macdonald's mating probability of distributions to be more dispersed than the Poisson, by assuming a negative binomial distribution of parasites in a host. The empirical conclusion of Bradley and McCullough's (1973) study was that the positive egg counts followed a log-normal distribution, implying rather fatter tails, and therefore even more irregular behaviour, than that obtainable from the negative binomial family. Their estimates indicate that, for the people in their study aged over 35, the number of eggs passed in 10 ml of urine was on average 27, with standard deviation 170. Yet, in a sense, even a ratio of 6.5 of standard deviation to mean understates the true variability they observed, since, assuming their estimated log-normal distribution, the largest egg counts they recorded came from a part of the distribution where the tail probabilities, although very small, were falling off very slowly indeed – locally, like a distribution with infinite mean and variance.

The effect of this is that, even in large populations, the values of sample averages tend to be unstable, depending to a noticeable extent on the large values obtained from a few individuals, and hence admitting considerable random variation. In Bradley and McCullough's data, 2% of the populace in any age group typically contributed 25% of the overall average output. This leads to the question of how, in constructing a model which is based on 'average' transmission rates, one should estimate the required averages. One way of deriving a more stable estimate of a typical count is to use the geometric mean of the egg counts, instead of the arithmetic mean. This procedure has its descriptive virtues, in that, if the logarithms of the egg counts are indeed normally distributed, the logarithm of their geometric mean is the best estimator of the mean of this normal distribution. However, transmission depends on the total number of eggs excreted per unit time, and not on a sum of logarithms, and if there is, in any practical sense, an average rate of output, it is estimated by the arithmetic mean of egg output, and underestimated by the geometric mean by a factor which, for Bradley and McCullough's data, is around 5. Thus one has really to accept that, even in populations of an

appreciable size, the random fluctuations in overall transmission remain significant, and that the unstable estimates of average rates obtained in practice are no more than a faithful reflection of this.

6.6 CONCLUSIONS

In the preceding sections, an attempt has been made to describe the transmission of schistosomiasis in mathematical terms. The results illustrate the way in which a mathematical description is able to draw attention to critical aspects of the assumptions being made, and to provide a framework within which to compare alternative hypotheses. Even the simple model of Section 6.2 proved useful in evaluating the effects of different methods of control; in particular, it was possible to show that the effectiveness of molluscicide for the purposes of eradication is very sensitive to the reductions in snail densities achieved, and to the searching ability of miracidia. Naturally enough, when making policy decisions between one control strategy and another, much more must be taken into account, not only in respect of the cost and feasibility of each strategy, but also with regard to their effects on other diseases and on the general level of amenity. Nevertheless, without the basic information provided by a model about what is attained or attainable by particular methods, it is much more difficult to come to good decisions.

The model of Section 6.2 was not only useful for evaluating the merits of control strategies, it also had its uses in clarifying how transmission is actually maintained. Its instability with respect to changes in its parameters, apparent even after the modifications of Section 6.3, was the reason for considering acquired immunity in the human host as possibly an important feature of the cycle. The subsequent analysis in Section 6.4 indicated that, both at Mwanza, Tanzania (*S. haematobium*) and at Malirong, Philippines (*S. japonicum*), human immunity was the most important natural factor in limiting the level of transmission.

Deterministic models were, by and large, found to be the most useful of the tools available, mainly because of their simplicity. However, many of the rate constants appearing in them were explained in terms of, or estimated by means of, an underlying stochastic model describing in detail a particular part of the transmission cycle. Two points of practical interest arose in the course of one such detailed analysis of the infection process. First, human hosts seemed to get infected rather more rarely than one would expect, and, second, there was empirical support for supposing that, in *S. haematobium*, immunity to further cercarial penetration became effective in the human host after two infections, and not just one. Finally, it was observed that assuming homogeneity of almost any kind has the effect of making transmission appear more marginally stable than in fact it really is, and that it is therefore necessary to take careful account of heterogeneity when assessing the values of the parameters of a model.

This discussion of mathematical models for schistosomiasis is not intended as a survey of the subject; a recent review can be found in Cohen (1977). Instead, it gives a personal view of a particular case history in mathematical modelling, designed principally to illustrate how simple models can be used effectively. As is inevitable with a large and complicated system such as the transmission of schistosomiasis, the argument has evolved out of the vast corpus of knowledge and ideas built up by previous work. But it is precisely when faced with such complexity that mathematical models are at their most powerful; they clarify the effects of, and relationships between the different elements of the system.

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