A TRANSMISSION MODEL FOR *SCHISTOSOMIASIS MANSONI* WITH AGE DEPENDENT EXPOSURE

THESIS

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A B S T R A C T

The aim of this project is to formulate a model for the transmission of Schistosomiasis, to obtain values to be used as parameter estimates, and to study the model's behaviour.

The use of a differential equation in modelling the transmission of Schistosomiasis was pioneered by Macdonald (1965a). His paper leaves some aspects unclear and an attempt is made herein to clarify that model. The basis for Macdonald's assertion that the effects of altering exposure and snail factors are similar is studied, as well as the lack of responsiveness to changes in contamination. A graphical technique to explore the asymptotic behaviour of this formulation is outlined. Work by Nåsell and Hirsch is discussed and an extension of their model incorporating age dependent exposure is described.

From studies in St Lucia, parameter estimates are obtained and their appropriateness discussed. The model's behaviour is explored by comparing observed and predicted results, by investigating the asymptotic levels of infection, and by studying the sensitivity of asymptotic levels to changes in parameters.

Macdonald's "breakpoint" phenomenon is not observed, mostly due to the immigration of infection. The proportion of snails patently infected is consistently overestimated. The predicted infection levels for different age groups fail to resemble empirical findings satisfactorily. Tactical questions are raised as to which specific

mathematical steps reflect different control strategies. An example is presented whereby different approaches attempting to model molluscicide produce contradictory recommendations for optimal control strategy. Future work should deal more realistically with snail populations and an allowance for immune effects is recommended.

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Chapter One:- Mathematical Models and the Transmission of Schistosomiasis

The current state of technology owes much of its existence to the advancement of the sciences of physics and chemistry in the most recent centuries. The growth of these fields has been greatly enhanced by the ability to quantify with considerable accuracy various processes or systems. Underlying this quantification, one frequently finds the ability to describe a process by means of mathematical relationships.

Many would hold today that the state of the world, though technologically sophisticated, is not necessarily advanced. While the 'hard' sciences of physics and chemistry have grown, the human sciences such as sociology, psychology and possibly biology have not advanced as far. As these latter topics are more difficult to quantify due to much greater variability in the behaviour of some components, the lack of a mathematical basis may be associated with less dramatic progress.

Mathematical models are increasingly being studied in fields not directly related to physics and chemistry. The potential for such tools in the study of tropical hygiene occurred to Sir Ronald Ross in the late nineteenth century, who explored the transmission of malaria by means of a differential equation. The development of models for malaria and their acceptance naturally prompted the study of the dynamics of other tropical diseases, one of which is schistosomiasis.

Three species of schistosomiasis are mostly responsible for infection in man. These are Schistosomiasis haematobium (urinary schistosomiasis), Schistosomiasis japonicum and Schistosomiasis mansoni (both intestinal

schistosomiases). The transmission of all three is similar with slight differences. A full description of the biological and medical features is found in the book by Jordan and Webbe (1969). Aspects of the cycle relevant to mathematical models are mentioned below.

Beginning in the human (or "definitive") host, schistosome eggs (or ova, singular ovum) are released into the host's urine (for Schistosomiasis haematobium) or faeces (for Schistosomiasis japonicum and Schistosomiasis mansoni). If the wastes are deposited near or in water, a fraction of the ova hatch to produce an aquatic form: the miracidium (plural miracidia). It would not be surprising to find the number of miracidia are much less than the number of eggs released. Both eggs and miracidia may be either male or female.

Miracidia swim until they locate a snail (or "intermediate") host or they expire. Both sexes of miracidia require the same species of snail to continue the transmission cycle, but the species of snail differs with the species of schistosomiasis. Within the snail, an asexual multiplication occurs, hopefully to a great enough extent to compensate for losses incurred in transferring from human to snail and for losses to come in the return of infection to the human host. It is thought that the amount of infection produced by an infected snail is the same regardless of the number of miracidial penetrations after the first. After being infected, a snail does not immediately contribute to the transmission cycle. A "latency" period is observed after which a snail releases a new form of infection called a "cercaria" (plural cercariae) into the water. A snail in the latent phase is described as "prepatent", and one releasing cercariae is "patent". As before, cercariae may be

male or female, depending on the sex of the infecting miracidium.

The infection is passed to man when human skin is exposed to infected waters during bathing, washing or other activities. For Schisosomiasis haematobium , non-human definitive hosts provide an alternate pool of infection, but this phenomenon, while not unknown, is thought to be of minor importance for Schistosomiasis mansoni and Schistosomiasis japonicum. Within the definitive host the cercaria undergoes various transformations to become a schistosome: the "worm" form.

The sexual aspect of the infection is critical at this stage: both male and female schistosomes are needed to produce eggs and thus complete the cycle. As well, in contrast to the phase of transmission in the snail, the more worm pairs a definitive host harbours, the more eggs are released ("super-infection"). The specific nature of the relationship between egg release and worm pair count is poorly understood at present.

It is seen that some aspects of this transmission cycle are capable of mathematical treatment, such as the multiplication in snails or the requirement of pairing in human hosts. Other aspects, less readily described mathematically might be approximated, such as the transfer of infection from definitive host to snail and vice versa. It was not until early in the sixties that attempts to exploit this approach were first published. Two of the pioneering papers were by Macdonald (1961) and Hairston (1962). With a life cycle involving several steps, a very natural problem is to seek the optimal technique

to minimize or eradicate transmission. In 1965, Macdonald (1965a) proposed a model based on a differential equation and studied the effects of various intervention schemes by altering the parameters of the model.

In his formulation, Macdonald (1965a) incorporated four "factors". These were: exposure, snail, longevity and contamination factors. By changing the values of these factors, and studying the effect on the eventual mean worm load in the human population, Macdonald investigated his formulation. It was concluded that the effects of reduction in the contamination factor produced negligible reduction in transmission. Another observation was that like changes in the snail and exposure factors produced almost identical changes in the mean worm load of the humans. Unfortunately, it is not clear from his description exactly how Macdonald modelled transmission and how the various factors were involved. In the second chapter, this formulation and these qualitative conclusions are investigated.

Another qualitative aspect which Macdonald (1965a) noted was termed the "breakpoint" behaviour of transmission. The "breakpoint" was a critical level of infection , and if the community level of infection could be reduced below this threshold, then eradication would occur. This phenomenon is a result of Macdonald's allowing for the bisexual nature of the worm and specifying that only a fraction (which itself depended on the mean worm load) of the worms in a human population were paired and capable of contributing to infection. This property of the model had an important epidemiological ramification: by reducing infection to a sufficiently low level, eradication spontane-

ously occurred. The alternative would be eradication through elimination of all instances of infection.

There have been several other attempts to describe mathematically the transmission of this disease. A paper by Cohen (1977) provides an interesting summary. Even a cursory study of the topic will lead to the conclusion that models cover a wide range from purely theoretical considerations to mostly empirical formulations. With this project, an attempt is made to take a theoretical model and make minor alterations. Rather than study the mathematical ramifications of the altered formulation, a set of parameters is obtained and the model's empirical behaviour is studied. The underlying intentions of this exercise are to investigate the empirical validity of this theoretical model and to decide if additional factors are warranted.

Chapter Two:- The Macdonald-Näsell-Hirsch Model

Two disciplines have been influenced by Macdonald's 1965(a) paper. Epidemiologists have accepted the conclusions reached by the author, and even now much store is placed by these. A few years after publication, mathematicians took up the challenge to model the transmission of Schistosomiasis, and several based their work on Macdonald's ideas. Indeed, a signal contribution to the study has been made by Näsell and Hirsch (1973), employing a model extending that of Macdonald.

Since the original publication, and particularly after Macdonald's death in 1967, there has been speculation as to whether conclusions he reached are general properties of his model or specific results of the parameters he had chosen. It is not possible to resolve these uncertainties from the information provided in the article. While several values are mentioned, insufficient information is provided to enable a replication of the calculations.

A search of the Macdonald papers in the Ross Institute has provided a few clues. The model described in 1961 differs considerably from that in 1965, and it was impossible to declare to which stage of development any particular script related. There was no definitive manuscript easily shown to be the basis of the 1965 paper and thus alternatives need to be considered in some of the steps that follow.

This chapter will attempt to summarize one set of parameters for Macdonald's simulations. From this, it will be possible to explore the sensitivity of the model (and conclusions especially) to parameter

values. As well, a graphical technique will be presented, enabling one to study the equilibrium situation for any set of parameters without numerically simulating the growth or decline of the population. Lastly, reference will be made to the main Nåsell-Hirsch extension, and Macdonald's parameters will be related to those of Nåsell and Hirsch.

1) The Macdonald Formulation

Wishing to keep notation as close to that of the 1965 paper, let us begin with population of P people, carrying a mean worm load of m worms per person in an isolated homogenous ecological complex. Of these Pm worms in the human hosts, only a fraction, $\alpha(m)$, are paired. The fraction depends on the mean worm load itself by the function:

$$\alpha(m) = 1 - e^{-m}\left\{1 + \left(\frac{m}{1!} + \frac{m^2}{2!}\right)\left(\frac{2!}{1!1!2^2}\right) + \left(\frac{m^3}{3!} + \frac{m^4}{4!}\right)\left(\frac{4!}{2!2!2^4}\right) + \cdots\right\}$$

This is based on the assumption that worms are distributed among humans according to a Poisson distribution. Nåsell and Hirsch have noted that a closed form for $\alpha(m)$ is given by:

$$\alpha(m) = 1 - e^{-m}\{I_0(m) + I_1(m)\} \qquad \text{(II-1)}$$

where $I_0(m)$ and $I_1(m)$ are Modified Bessel Functions of the zeroeth and first order respectively. The dimensions of $\alpha(m)$ are paired worms per worm.

The P people make E entries per day per person into the water uniformly along a river L meters long, during which they both contaminate and are exposed to infection. Along the riverbank is found a snail population of density S snails per meter, giving a total of SL snails.

The specific approach which Macdonald used to determine the total daily production of ova from the paired female schistosomes is unclear and two alternatives are worth consideration. In one approach, a paired female schistosome is assumed to produce a known total number of eggs (denoted by e) in her lifetime. By assuming the schistosome's survival is exponential and the number dying is r schistosomes per day, then the mean lifespan of a paired female is $[-\log_e(1-r)]^{-1}$ or approximately r^{-1} for small values of r. Thus the number of eggs released per day is er. Of these er eggs released per paired schistosome daily only a fraction reach the water per entry. The alternative approach is to simply assume a paired female schistosome produces z_1 eggs daily and a fraction of these reach the water per entry. The important distinction between these approaches, as will be seen below, is that one involves the parameter r and the other does not.

On each day, there are PE entries and PEmα(m) paired worms are available to release ova. The number of miracidia available daily from each paired schistosome is given by k_1z_1. As an egg gives rise to either one or zero miracidia, the fraction k_1 is one half the proportion of eggs producing miracidia. It is assumed that exactly one half of the paired schistosomes are female and thus capable of producing eggs.

Only a fraction of the miracidia succeed in infecting snails. Macdonald tersely assumed the fraction successful was related to the snail density by the function:

$$1 - e^{-0.1S} \qquad \text{(II-2)}$$

and alluded to the work of Chernin and Dunavan (1962). The basis for this is hard to trace, both the form of the function and the choice of

the value of 0.1.

At first sight, the function appears to result from a probabilistic argument involving the Poisson distribution, where $e^{-0.1S}$ is the probability a miracidium is not successful. (This is particularly attractive bearing in mind the important role played by Poisson assumptions in Macdonald's pairing considerations.) However, it is difficult to specify an underlying process. A stochastic argument would involve a certain concentration of miracidia in the water and the events would be the number of snails infected within a fixed time. This does not readily yield the probability that a miracidium gives rise to an infected snail. Chernin and Dunavan considered systems involving a single snail and a single miracidium as well as alternatives with five snails and a single miracidium and five miracidia and one snail. In all cases, the event to be noted was restricted to a binary response: either a specific miracidium was successful or a specific snail was infected. Macdonald possibly chose the function for the lack of any preferred alternative and the similarity it bore to a stochastic styled argument was inconsequential.

The basis for selecting 0.1 is unclear as well. When this probability is used to obtain expected success rates in Tables I and II of Chernin and Dunavan, the values consistently overestimated the observed success rates. The fraction of miracidia successfully infecting sn ils may be overestimated, but the effects of this need to be considered with the possibility of underestimation of $(k_1 z_1)$. In a later part of this chapter, implications of the use of $1 - e^{-0.1S}$ are further considered.

With PE $(k_1 z_1) m a (m)(1 - e^{-0.1S})$ successful miracidia per day, Macdonald described the total daily inoculation rate (per snail) as:

$$B m\alpha(m) = \frac{PE(k_1 z_1) m\alpha(m)(1 - e^{-0.1S})}{SL} \quad . \qquad \text{(II-3)}$$

Above, it was noted that different treatments of some sections of Macdonald's model exist. In 1961, Macdonald's inoculation rate of snails differed from that employed in 1965. In the earlier version allowance was made for the death of miracidia whereas the later formulation only considered miracidia released in the same day. Furthermore, the proportion of miracidia successfully locating snails was independent of the snail density in the earlier work and the work of Chernin and Dunavan prompted the use of $1 - e^{-0.1S}$ in 1965.

A steady state argument is used to determine the infection "rate" (really infected proportion) of snails. This is quite similar to that employed in Macdonald's Malaria model (1957). If the probability that a snail survives one day is p, and survival is assumed to be exponential, then the steady state proportion of snails infected is:

$$\frac{B m\alpha(m)}{B m\alpha(m) - \log_e p} \quad . \qquad \text{(II-4)}$$

The lag time of n days after which an infected snail releases cercariae (thus contributing to transmission) is again handled analogously to that in the Malaria model, and the proportion of snails "patent" (cercaria releasing) is:

$$\frac{p^n B m\alpha(m)}{B m\alpha(m) - \log_e p} \quad .$$

The number of cercariae released daily per patently infected snail is z_2 . Furthermore, cercariae are assumed viable only within one meter and each person makes E/L entries per day in any particular meter. The

number of new infections per person daily from one patently infected snail is $E(k_2z_2)/L$. As a cercaria either succeeds or fails to give rise to a new schistosome in the human host, k_2 is the proportion of cercaria producing new infections.

The inoculation rate per person per day is thus:

$$h = \frac{ABm\alpha(m)}{Bm\alpha(m) - \log_e p}$$

$$= \frac{SPE^2(k_1z_1)(k_2z_2)p^n(1 - e^{-0.1S})m\alpha(m)}{PE(k_1z_1)(1 - e^{-0.1S})m\alpha(m) - SL\log_e p}$$

where

$$A = p^n(k_2z_2)SE \ .$$

Allowing the worms to die at the rate of r per day, then the daily change in mean infection (dm/dt) is related to m by:

$$\frac{dm}{dt} = \frac{ABm\alpha(m)}{Bm\alpha(m) - \log_e p} - rm \ . \qquad \text{(II-5)}$$

The integral of this differential equation describes the transmission of the parasite.

2) Parameter Values

Specific values for parameters can be found in several places in Macdonald's paper. As well, a listing of the computer programme believed used in the simulations has been found, containing values ascribed to the "Standard" situation. The programme was written in a high level language called EXCHLF and run on an Atlas computer. The

input values do not correspond for the most part with the specific parameters mentioned above (such as L, E, P and so on) but rather to collections of these. Indeed, even A and B are computed from the input parameters.

The method of approximating the curve of m(t), where t represents time, was a first order approximation. The mean worm load was calculated daily from the previous day's values, i.e.:

$$m(\tau + 1) = m(\tau) + \left.\frac{dm(t)}{dt}\right|_{t=\tau} .$$

In Table II-1, the input values and parameters (Y_0 to Y_6) as found on the EXCHLF listing are reproduced. The values correspond to Macdonald's "Standard" curve. The last column represents the suspected interpretation and will be discussed below.

Before attempting to identify values for specific parameters based on these seven input values, it is instructive to explore which of Y_0 to Y_6 can be altered to produce Macdonald's published figures. In this way, alternative formulations of the model may be eliminated. Within the computer program the values of A and B were obtained from:

$$A = Y_0 \times Y_6 \times Y_2^{Y_6}$$

$$B = \frac{Y_1 \times (1 - e^{-0.1 \times Y_6})}{Y_6} .$$

Macdonald described four factors: snail, contamination, exposure and worm longevity. Two of these are readily identified and two are not.

The snail density factor is clearly S. Runs changing Y_6 from the

"Standard" value of five to double, one fifth and one fifteenth this faithfully reproduce Macdonald's results in his Figures 2 (Curve C), 3 (Curve B) and 5.

The contamination factor is one component of parameter k_1 . Runs changing Y_1 as specified by Macdonald reproduce his published curves.

The exposure factor, at first consideration, might be taken as the parameter E. Unfortunately, this parameter occurs twice in the above formulation as people are assumed both to contaminate and possibly to pick up infection during each entry. (This treatment of E is a weakness in the formulation. The parameter could easily have been split into E_1, the daily number of entries resulting in contamination, and E_2, the daily number of entries during which the human was subject to risk of infection.) If the exposure factor is E, then values of Y_0 and Y_1 must be adjusted. Alternatively, considering k_2 to involve the exposure factor alone, the dual task of E is avoided. Hence runs are made changing Y_0 alone and Y_0 and Y_1 concomitantly, and the results (curves b_1 and b_2 respectively in Figure II-1) have been compared with Macdonald's curve B, in his Figure 3. It is concluded that b_1 is preferred to b_2 , and that the exposure factor is taken to be parameter k_2 .

The longevity factor is assumed to be parameter r, but there is ambiguity as to which factors of Y_0 to Y_6 involve r. As noted above, the determination of daily ova production per paired female has not been handled consistently. While changes in r would be reflected by changes in Y_3, it is unclear whether or not Y_1 should be altered simultaneously. (This would be so if e were fixed so that $z_1 = er$ was proportional to r).

As before, both alternatives were studied, and comparison of curves c_1 (Y_3 altered alone) and c_2 (Y_1 and Y_3 together) with curve C of Macdonald's Figure 3 indicate Y_3 is used in the published model. As a result, the z_1k_1 argument mentioned above has been chosen in preference to that involving r. It is worth noting that contrary to other factors, longevity is "reduced" by increasing the value of r, and not decreasing it. As r represents the proportion of schistosomes dying in one day, a reduction in mean life span from 1,000 to 200 days involves increasing r from 0.001 to approximately 0.005. (This exact value adequately reproduces the published figures.)

Table II-2 summarizes the relationship between the four factors, the parameters and input values for the original programme. Some reliance is gained as it is possible to reproduce most of Macdonald's remaining Figures. Unfortunately, it proves impossible under this formulation, to reproduce Macdonald's Figure 4 from the values cited in the original paper. The existence of a breakpoint and the properties ascribed to it in the text are observed, but the numerical values quoted do not bracket the breakpoint for either contamination of snail factors. Figure II-2 demonstrates the effect of reducing longevity to one fifth and then lowering contamination as well. A reduction of contamination to two thirds does not lead to eradication, but further reduction to three fifths does.

While the ability to reproduce most of Macdonald's Figures strengthens one's belief that the above formulation is that used by him, nevertheless the inability to reproduce Macdonald's Figure 4 leaves the formulation still open to doubt.

3) Individual Values of Parameters

From specific references in the 1965a paper and values obtained from other manuscripts, it is possible to recover most of the values of individual parameters in Macdonald's model.

As mentioned in Table II-1, the values of S, p, n, and r are reasonably assumed to be 5 snails per metre, .95 snails surviving per day, 25 days latent and one thousandth of all worms dying daily.

On different sheets, the values of P and L are both given as one thousand (people and meters respectively). Thus, the human and snail populations have values of 1,000 and 5,000 respectively.

On page 493, paragraph one, line six, Macdonald claims each paired female schistosome produces 1,000 eggs daily, hence providing us with z_1 . The contamination factor is given on page 497, paragraph five, line five as 0.001. At this point, it is unclear how this value relates to k_1, and what assumptions are involved in this choice. It was noted above that k_1 incorporates a factor of $\frac{1}{2}$ as this is the fraction of paired worms capable of producing eggs. From Table II-1 we have the relation

$$Y_1 = \frac{(k_1 z_1)EP}{L} = 1.25$$

and there is an inconsistency if we assume all factors but E are known. For then E is solvable, whereas on page 497, paragraph five, line six, Macdonald states, "No specific figure has been given for the number of water entries per person per day, but the total exposure factor previously described, which included a still unmeasured biological constant, has been adjusted to produce what is thought to be a realistic result".

Thus, from the ambiguity concerning k_1, we are left with the relation $k_1E = 1.25 \times 10^{-3}$, and can say nothing of k_1 and E separately except that the former incorporates the contamination value of .001 and other effects.

Similar ambiguities are noted in attempting to separate the values of E, k_2, and z_2. The "unmeasured biological constant" in the quotation from Macdonald in the paragraph above may allude to the k_2 factor. Indeed, the text immediately following is: "The value used is 0.02, which would mean that, with an average of one entry daily per person, scanning one metre of water, the probability of the individual cercaria within that square metre successfully penetrating would be 0.02, though the actual values used are quite immaterial to the present context". (Macdonald possibly thought of a water course L metres long and one metre wide and hence used a scanning of one square metre.) Again from Table II-1, one has:

$$Y_0 = E(k_2z_2) = 0.015 .$$

By assuming $k_2 = 0.02$, one is left with $Ez_2 = 0.75$ and, as before, unable to deduce anything more specific concerning E or z_2 . This value of Ez_2 is described by the preceding discussion as the product of the number of daily entries and daily release of cercariae per snail. A value of 0.75 for this is possibly too small, and one is left to conclude that the interpretations of z_2 and E cannot be separated clearly.

Table II-3 summarizes the values of Macdonald's parameters. Below it is noted that despite the inability to resolve E, k_1 and z_2, one is able to obtain estimates for use in other models.

4) Sensitivity of Macdonald's "Standard" Situation

Two properties of Macdonald's model are that, in terms of the equilibrium mean worm load, the snail and exposure factors are similar in effect, while changes in the contamination factor produce little alteration in the results. With the above formulation and explicit values for the parameters, it is possible to examine the data specific or model specific nature of these results.

The similarity in effects of snail and exposure factors can be traced to the assumption that the proportion of successful miracidia depends on the number of snails given by equation II-2. Expanding the exponential, one has:

$$\frac{1 - e^{-0.1S}}{S} = 0.1 - 0.005S + 0.0001667S^2 - \cdots$$

a term used in obtaining B. The effect of doubling the exposure factor, k_2, is a doubling of A, leaving B,p and r unchanged. Doubling the snail factor, S, likewise doubles A, but has very little effect on B for the values chosen (not more than 10 snails per meter). Parameters p and r are unchanged as before. Thus, as B in this formulation is relatively insensitive to S, and both snail and exposure factors affect A similarly, therefore they have similar effects on the equilibrium mean worm loads. The equivalent effects are a result mostly of the model formulation and less of the choice of parameter.

The insensitivity of the results to the contamination factor cannot be traced to a specific assumption in the model, and is mostly a result of the choice of values for parameters. This is examined by studying the effect of changing each parameter (with all others held

constant at the "Standard" value) on equilibrium mean worm load.

Figure II-3 shows the relation between equilibrium mean worm load and different values of r. By changing the mean life span from 1,000 days to 200, it is apparent that a large reduction would be predicted, while a further reduction to a lifespan of 100 days would lead to eradication.

Figure II-4 presents similar relations for the other factors, both for the case when longevity is "Standard" (mean life span of 1,000 days) and when longevity is reduced to one fifth by a chemotherapy programme. Not surprisingly, the snail factor and exposure factor exhibit similar behaviour. The equilibrium mean worm load is sensitive to changes in these factors, and the effect of chemotherapy is a radical change in the point of eradication. In particular, the population is supported when factors are reduced to one fifth if r is 0.001, but chemotherapy (r = 0.005) shifts the point of eradication to the other side, and no population is predicted. This is shown in Macdonald's Figures 3 and 5.

The curve for the contamination factor is different from all others, and it is apparent that changes in this factor about the "Standard" level have little effect on the equilibrium situation. Indeed, in constructing his Figure 5, Macdonald chooses a situation where contamination is near to having an effect. A further reduction to one twentieth would have lead to quite different conclusions!

For biological interpretations, it is of interest to compare the effect of changing contamination on the proportion of snails infected. These are split in Table II-4 into those only releasing cercariae

("patent") and all infected, including those "prepatent". The percentages are fairly high, and for the "Standard" situation, relatively insensitive to the contamination factor. When a chemotherapy campaign is considered, the equilibrium worm load is more sensitive to the contamination factor.

5) Graphical Study

Even without knowledge of Macdonald's specific formulation, it is possible to study the equilibrium situation without recourse to numerical integrations.

Consider setting the differential equation equal to 0 (thus assuming that the equilibrium values are reached) and solving for Macdonald's pairing proportion:

$$\alpha(m_\infty) = \frac{r(-\log_e p)}{B(A-rm_\infty)}$$

As functions of the equilibrium mean worm load (m_∞), the lefthand side is given by equation II-1 and the right-hand side is a rectangular hyperbola with a vertical asymptote at

$$m_\infty = \frac{A}{r} .$$

For clarity, the former curve is termed the "pairing" curve, and is independent of the parameters A,B,p and r, while the latter is called the "parameter" curve, and depends on all four parameters.

Both curves are plotted on the same axes, and by studying the changes in values of m_∞ at the intersections with alterations in various parameters, one can study the change in both breakpoint and equilibrium

mean worm load. Figure II-5 presents the three possible alternatives. Whenever the parameter curve drops below the pairing curve, the value of dm/dt is positive. Thus, for curve I in Figure II-5, any value of m betweem m_a and m_b will increase to m_{∞} at m_b, where the intersection indicates an equilibrium state. In the event that m exceeds m_b, then dm/dt is negative and m will decrease eventually to become m_b. Furthermore, any slight perturbation about m_b will lead to a return to m_b, and thus this is termed a stable situation. The other intersection at m_a behaves differently. A mean worm load above m_a suggests $dm/dt > 0$ and a growth to m_b. A mean worm load below m_a suggests the opposite, and a decline to eventual eradication. In the unlikely event that a situation occurs whereby a mean wormload of m_a exists, then any slight perturbation leads to growth or eradication. Thus, m_a is termed an unstable equilibrium and is indeed Macdonald's breakpoint.

Curve II of Figure II-5 presents the unlikely situation wherein the pairing and parameter curves meet in only one point. While an equilibrium population is feasible at m_c, any slight perturbation below m_c will produce eradication.

Curve III of Figure II-5 presents the case whereby neither curve intersects. In this situation, there is no possibility of any population being established.

There are two approaches to eradicating a population of schistosome worms, according to this formulation. If a population exists, then one assumes the situation is modelled by curve I of Figure II-5. It is possible to eradicate the population by reducing the mean worm load to below m_a. While this may provide temporary benefits, there is still

the opportunity for the population to regain its former status at m_b (possibly through sufficient immigration of worms). Alternatively, by changing the parameters of the parameter curve to produce a switch from the curve I situation to curve III, the breakpoint is "washed out", (and with it the possibility that m_∞ is greater than zero), and there is no hope for re-establishment of the infection.

Lastly, this graphical approach lends itself conveniently to consideration of pairing curves other than Macdonald's. The effect of clumping, as studied extensively by May (1977), can be incorporated in calculating the pairing curve, and similar heuristic results to those above still hold. Figure II-6 presents Macdonald's "Standard" parameter curve with May's two clumping situations. (These will be more fully described in Chapter IV.)

6) The Nåsell-Hirsch Model and Macdonald's Values

In 1973, Nåsell and Hirsch published a model of the transmission cycle for schistosomiasis. From a series of strictly defined mathematical assumptions, a stochastic formulation was described. Whereas Macdonald dealt deterministically with mean worm loads and proportions of snails infected, Nåsell and Hirsch derived the probability distribution of worms within a host and the distribution of infected snails. Unfortunately, a fully stochastic formulation proved intractible, and a "hybrid" solution was proposed. (The term "hybrid" implied that the model contained some stochastic and some deterministic elements.) The model was cast around the expected proportion of infected snails and a variable close in meaning to the expected mean worm load.

The dynamics of the Nåsell-Hirsch model were studied by use of a

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The dynamics of the Nåsell-Hirsch model were studied by use of a

system of two differential equations. (The relations between this system and Macdonald's equation are described by May (1977).) The authors demonstrate that consideration of the effects of various parameters can be linked to considerations involving two "transmission factors" T_1 and T_2 . These are composites of the other parameters in the model. The existence and nature of critical points in their model is studied extensively with particular reference to these transmission factors. The relevance of aspects of the model to epidemiology and control is examined in a concluding section of their paper. Since publication of this model, Nåsell has studied the effects of modifications on this formulation such as allowing for snail latency (Nåsell, 1976a), external infection (Nåsell, 1974), and immunity (Nåsell, 1977b).

In 1977 Nåsell (1977a) published an article questioning some claims by Macdonald that his 1965 conclusions were model dependent, and not value or parameter dependent. It is possible to calculate parameters for the Nåsell-Hirsch model from Macdonald's "Standard" situation, enabling one to study the data dependency as suggested by Nåsell as well as to study the effect of introducing the second differential equation to the model.

The instantaneous (which, following Macdonald, is here assumed to mean daily) death rates for schistosomes and snails, denoted as μ_1 and μ_2 respectively, are obtained directly. Obviously $\mu_1 = r = 0.001$. Macdonald assumes that snails exhibit exponential survivorship and that p snails (a proportion) survive one day. Hence:

$$p = e^{-\mu_2} = 0.95$$

or $$\mu_2 = -\log_e(.95) \approx .0513 .$$

Calculating the rates of acquisition of infection in snails and humans is less direct. Nåsell and Hirsch break down the instantaneous rate of infection for a given snail from a given schistosome pair into the daily production of viable miracidia per paired female schistosome (λ_1) and the probability that a miracidium successfully penetrates a given snail (p_2)

$$\nu_2 = \lambda_1 p_2 .$$

This is related to Macdonald's parameters by

$$\nu_2 = 2\frac{B}{P} .$$

The factor of two arises from Macdonald's tacit inclusion of a factor of $\frac{1}{2}$ in k_1 (as only half the paired worms produce eggs), and the exclusion of the factor in the Nåsell-Hirsch parameter. Despite the inability to specify values for each of Macdonald's parameters, one has:

$$\nu_2 = 1.967 \times 10^{-4} .$$

Nåsell and Hirsch break down ν_1, the probability that a given snail produces a new schistosome in a given human analogously to the split of ν_2. Where λ_2 is the number of viable cercariae released daily per infected snail, and p_1 is the probability that a cercaria infects a given human, then $\nu_1 = \lambda_2 p_1$.

Macdonald's use of probability of penetration in the same meter of riverbank (k_2) necessitates allowance for L to get the overall probability of success. One has $\lambda_2 = z_2$, and hence:

$$\nu_1 = \frac{E(k_2 z_2)}{L} = 1.5 \times 10^{-5} .$$

(Again, the inability to resolve $E(k_2 z_2)$ has not precluded calculation of ν_1.)

It is felt that in the spirit of a reasonable comparison, allowance for the prepatency is warranted, and thus:

$$\nu_1^* = \frac{p^n E(k_2 z_2)}{L} = \frac{A}{SL} = 4.161 \times 10^{-6} .$$

Lastly, the number of definitive hosts (humans) is $N_1 = P = 1{,}000$. The number of snails is $N_2 = SL = 5{,}000$.

If an initial Poisson distribution of worms is assumed, the relevant part of the Nåsell-Hirsch model for this comparison is:

$$\frac{dm}{dt} = \nu_1^* N_2 y - \mu_1 m$$

$$\frac{dy}{dt} = \tfrac{1}{2}\nu_2 N_1 \alpha(m)(1 - y) - \mu_2 y$$

where y is the expected proportion of snails patently infected and m the expected mean worm load. Substituting values, one has:

$$\frac{dm}{dt} = 0.0208y - 0.001m$$

$$\frac{dy}{dt} = 0.0984\alpha(m)(1 - y) - 0.0513y .$$

By considering two transmission parameters, T_1 and T_2, Nåsell and Hirsch demonstrate how to determine the existence of equilibrium solutions. For this example:

$$T_1 = \frac{\nu_1^*}{\mu_1} N_2 = 20.804$$

$$T_2 = \frac{\nu_2}{\mu_1} N_1 = 3.835 .$$

Figures II-7 and II-8 display the effect on the equilibrium mean worm load and breakpoint as T_1 is reduced with T_2 held constant and as T_2

is reduced with T_1 held constant respectively. It is apparent that changes in factors affecting T_1 (such as μ_1, ν_1^* and N_2 which would include Macdonald's longevity, exposure and snail factors) have noticeable effects for all values of T_1 . For T_2, however, a reduction to $\frac{1}{4}$ the standard value (analogous to Macdonald's contamination factor through ν_2) reduces the mean worm load by only 10%. Thus the insensitivity to changes in contamination for this choice of parameters is observed in the Näsell-Hirsch formulation as well as Macdonald's.

It remains to be seen if the two dimensional system produces different results from Macdonald's one dimensional equation. Both formulations produce similar equilibrium mean worm loads (20.171). As Macdonald's snail infection rate is the same as a steady state substitution in the two dimensional system (May 1977), the equilibrium proportions of infected snails are similar.

Lastly, the "phase space" between the mean worm load and proportion of snails infected is shown in Figure II-9. Macdonald's direct relation of proportion of infected snails to mean worm load (equation II-4) does not differ noticeably from the relationship obtained by computation in the two dimensional model. Thus, Macdonald, for his choice of parameters, does not seem to have lost much in only employing a one dimensional model.

While here there is little advantage in elaborating the model, such may not be the case with other parameter sets. Though more complicated mathematically, the two dimensional system involves no new parameters, yet is less restricted (by not making a steady state assumption for snail infections), and thus is to be preferred.

Another property that both models above share is that the mean worm load (or expected mean worm load) changes monotonically to the asymptotic value. If the eventual level is below an initial value, there is a monotone decrease, and if the eventual level exceeds that at the start, a monotone increase is predicted. Considering a host to be uninfected at birth, one thus predicts a non-decreasing growth of infection to an asymptotic level in endemic areas. Unfortunately, empirical data displays an increase in mean worm load (often termed "intensity of infection") to a peak in the teen age years followed by a decrease in older ages. Two explanations seem to predominate in explaining the observed unimodal shape: it is either the influence of an immune response, or that of an age dependent exposure rate.

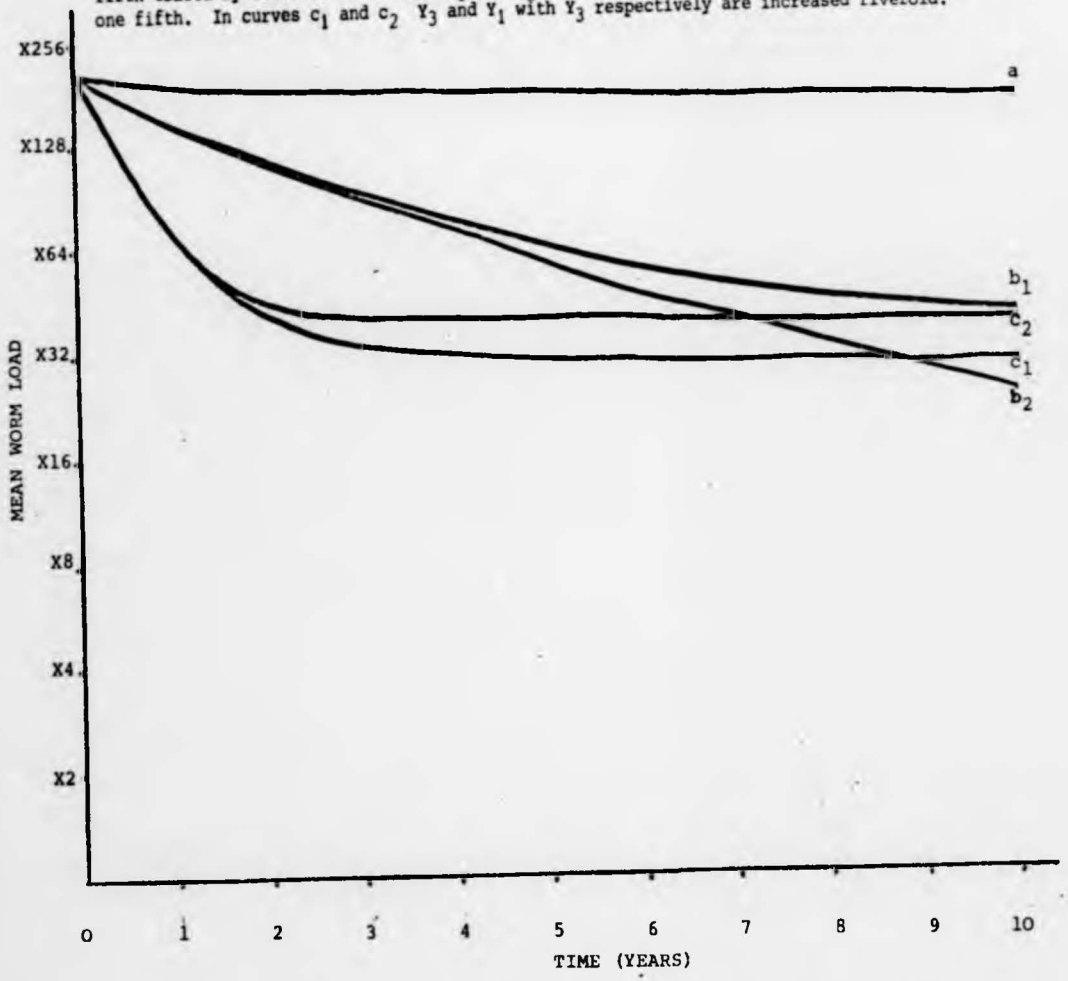
Models that allow for immune effects have been proposed by Barbour (1978), Lewis (1975a), Linhart (1968) and Nåsell (1977). As well, Hairston's formulations (1962, 1965) incorporate allowances for immunity.

A recent model proposed by Rosenfield and Jordan (1978) makes use of data on age specific exposure to infected water. This work is a further development of a model described by Rosenfield in 1975, and differs from the approach taken by Macdonald-Nåsell-Hirsch. The model is obtained from one of Muench's (1959) catalytic models. For each age group, the prevalence of infection in humans for a given year is predicted from the prevalence in the preceding year, the amount of exposure per contact and an estimated loss of infection. The intention of such work is less to model the nature of the flow of infection and more to obtain predictions relatively easily. To that end, little attention is paid to the intermediate stages of transmission (especially concerning the phase in snails)

and much use is made of regression estimates of relevant parameters.

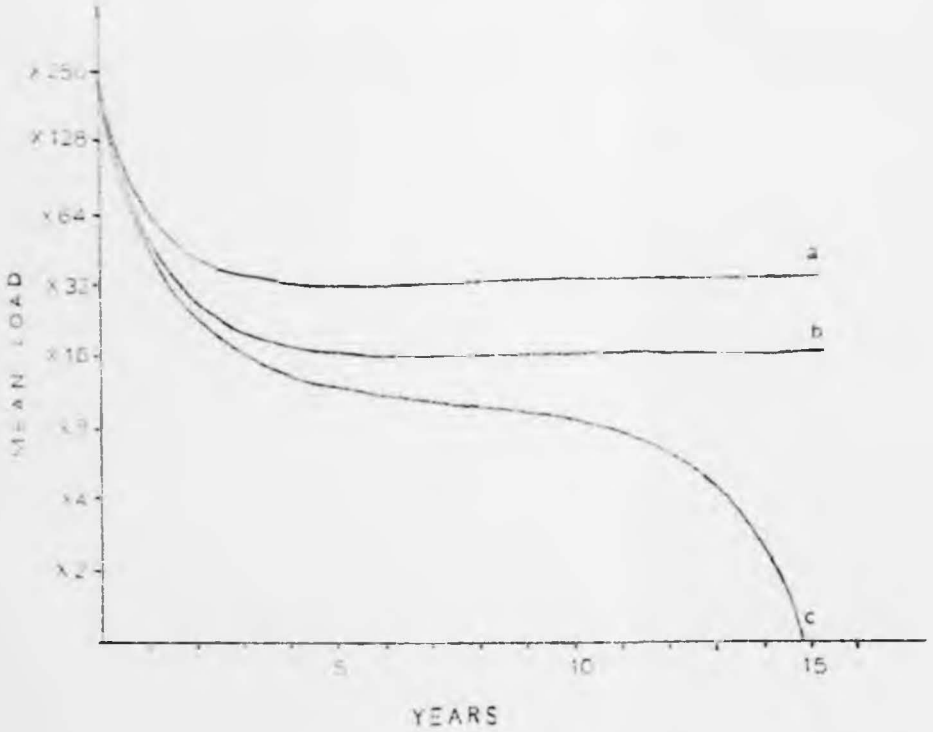
In what follows, the Macdonald-Nasell-Hirsch model is extended to allow different exposures per individual to infected waters for different age groups. Specific parameterizations are suggested based on ten years' data from a region in St. Lucia, West Indies, and the empirical nature of the formulation is investigated. One aim of this exercise is to investigate whether allowance of differential exposure alone produces predictions resembling empirical results.

FIGURE II-1 Compare to Macdonald's Figure 3. Effect of reducing contamination factor to one fifth traced by curve a. In curves b_1 and b_2 Y_0 and Y_0 with Y_1 respectively are reduced to one fifth. In curves c_1 and c_2 Y_3 and Y_1 with Y_3 respectively are increased fivefold.



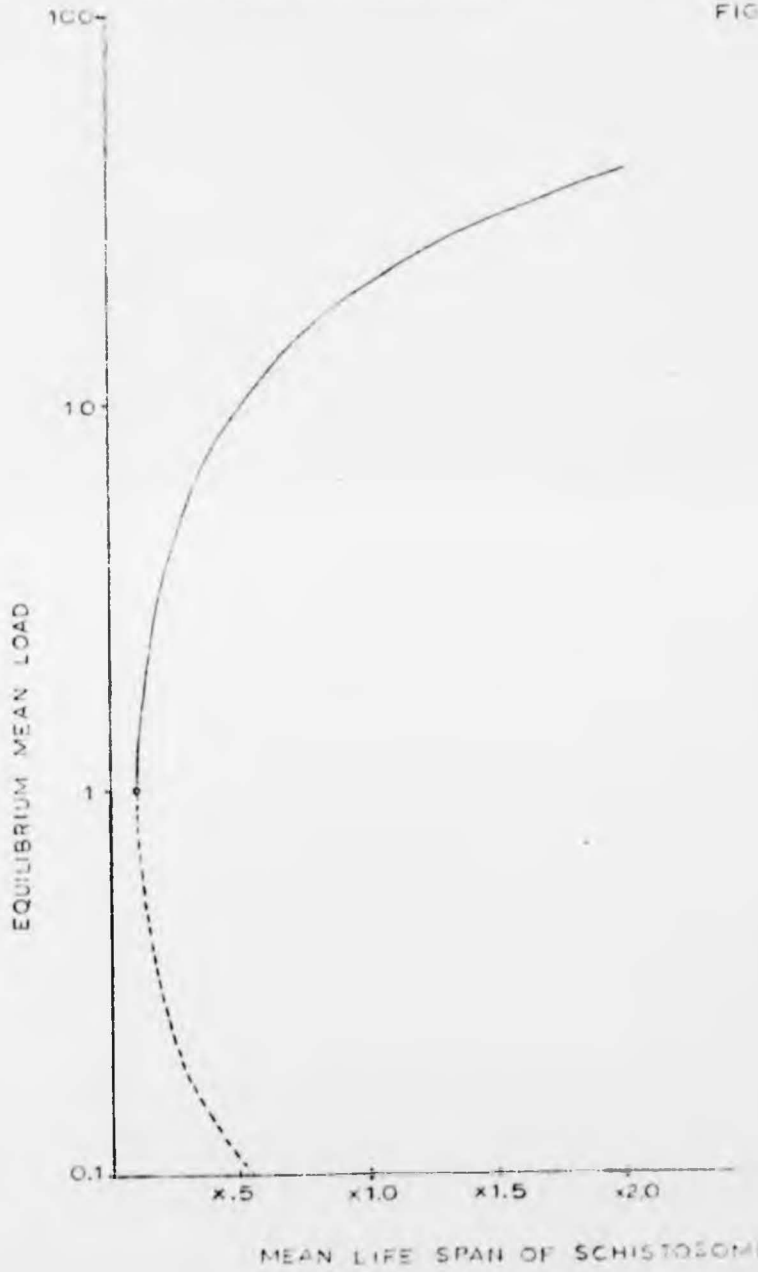
Compare to McDonald's Figure 4. Convexity clause is reduced to one fifth (a) then with contamination firstly to two thirds (b) and secondly to three fifths, bracketing the breakpoint.

FIGURE II-2



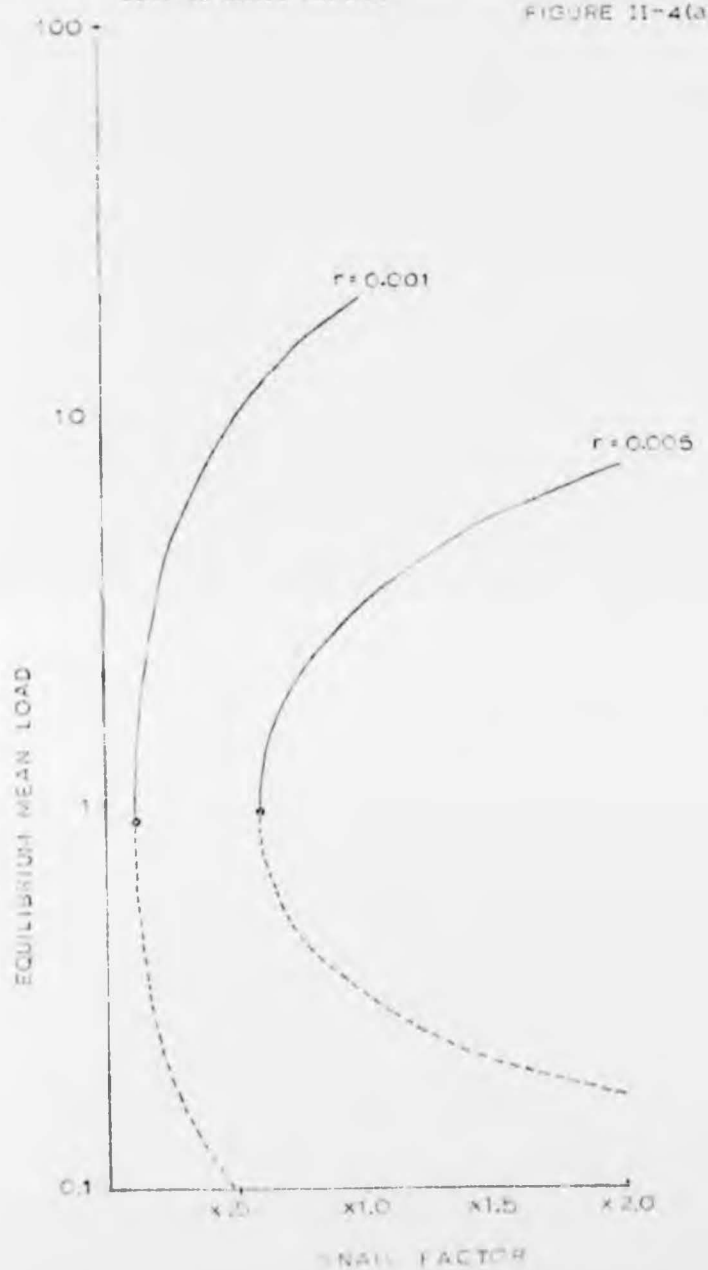
Sensitivity of equilibrium mean worm load to life span of schistosomes.

FIGURE II-3



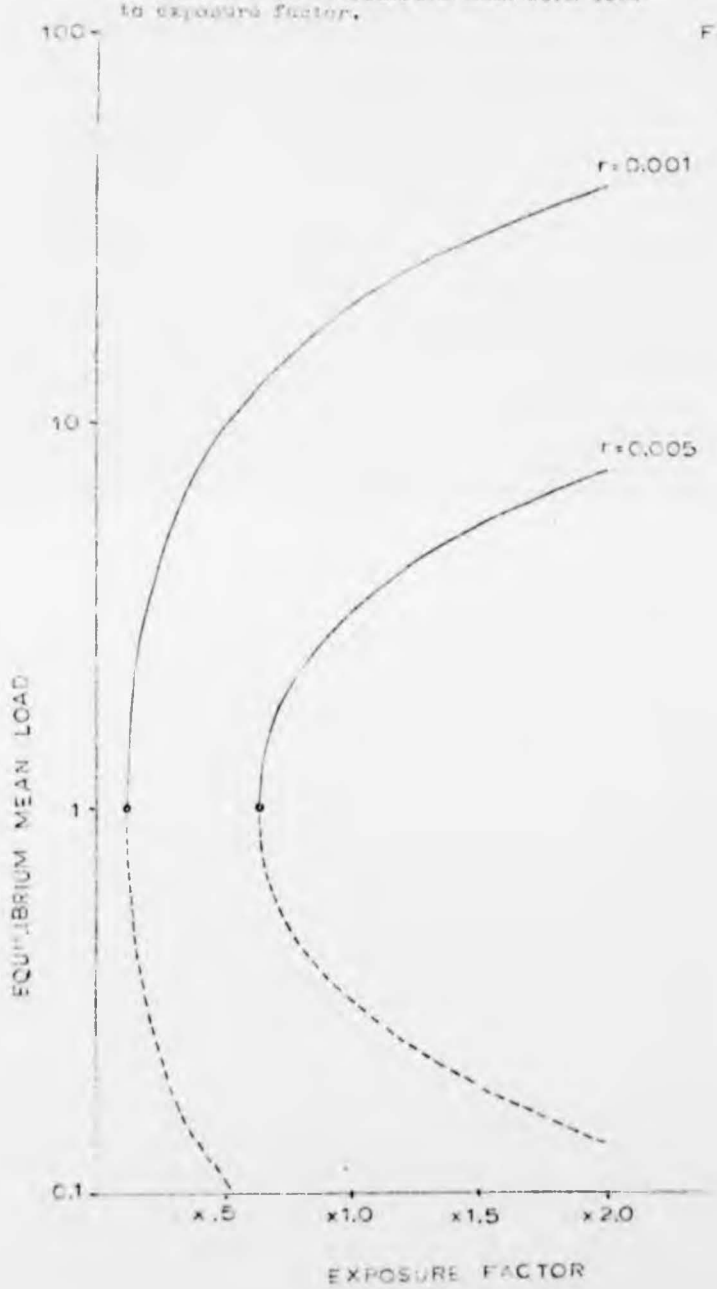
Sensitivity of equilibrium mean load to snail factor.

FIGURE II-4(a)



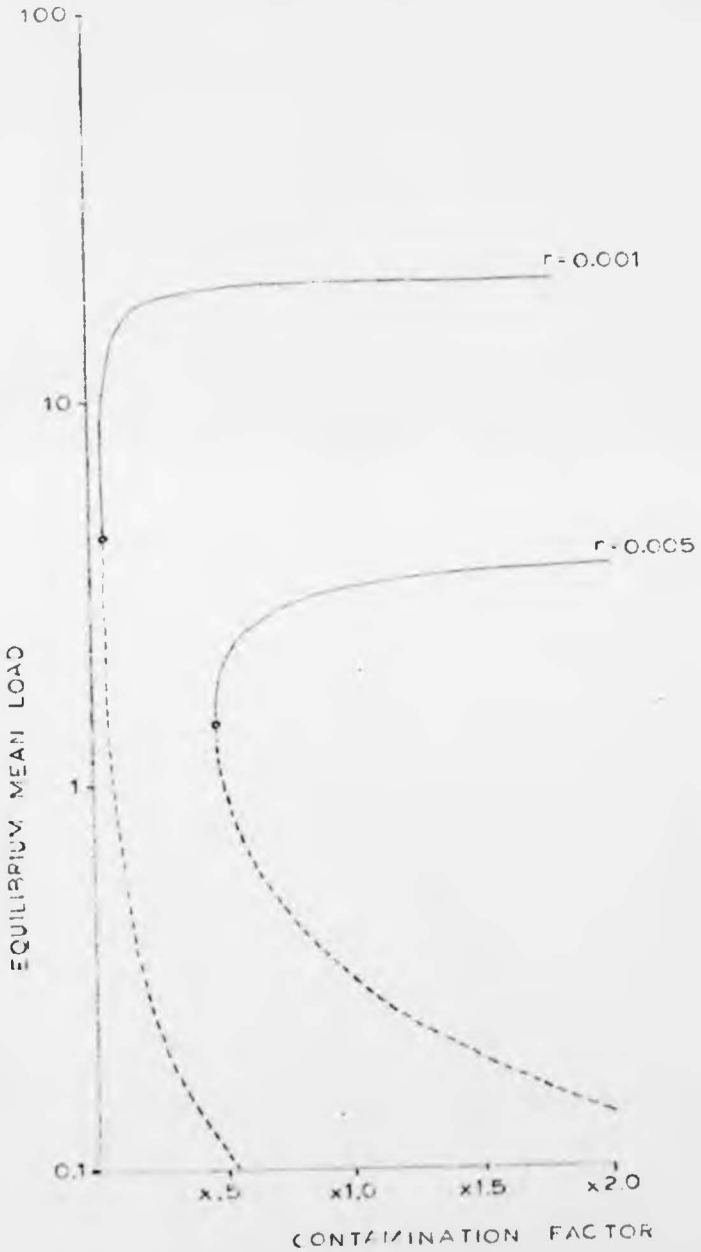
Sensitivity of equilibrium mean worm load to exposure factor.

FIGURE II-4 (b)



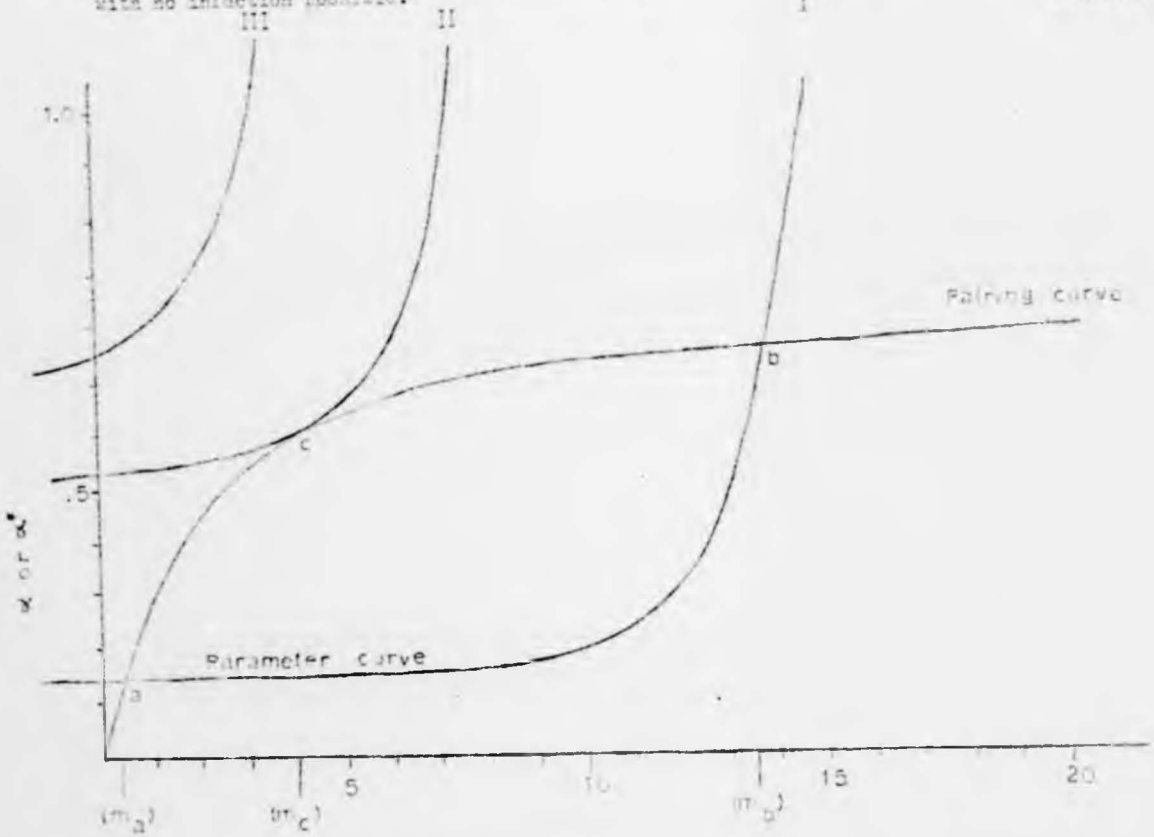
Sensitivity of equilibrium mean worm load to contamination factor.

FIGURE II-4(c)



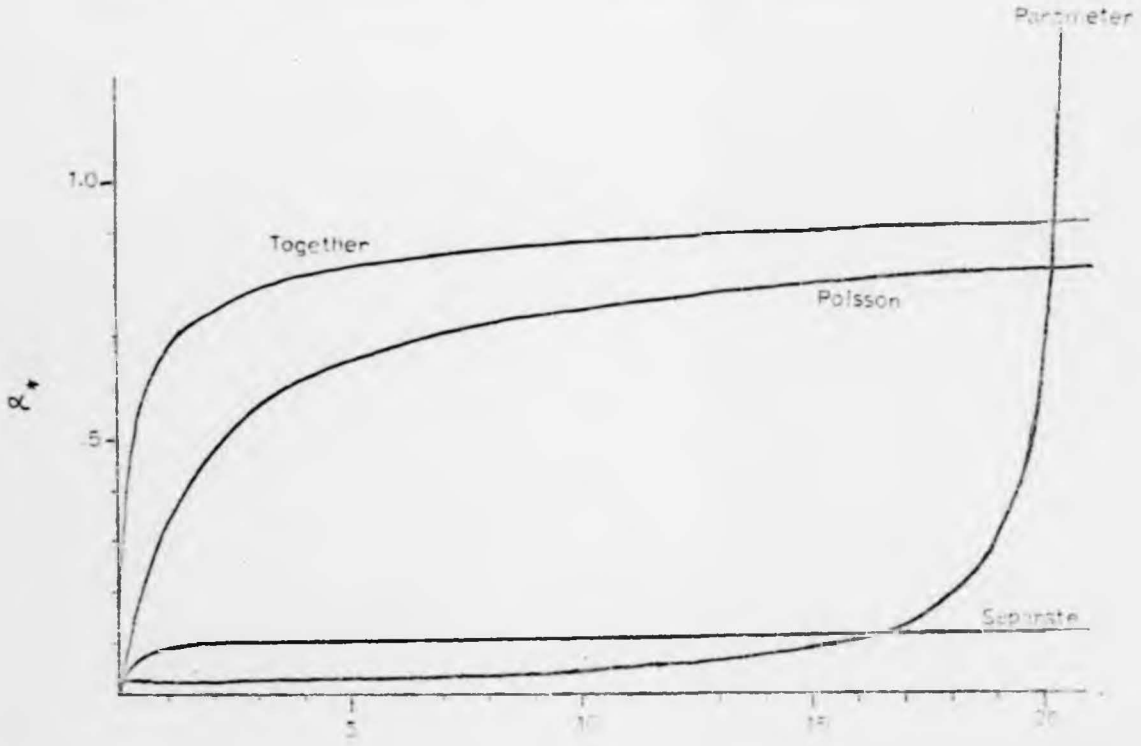
Graphical study of Macdonald's model. Curve I displays the situation where a stable population is possible at m_b (with breakpoint at m_a). Curve II displays the situation with an unstable equilibrium at m_c. Curve III displays "washout" with no infection possible.

FIGURE II-5



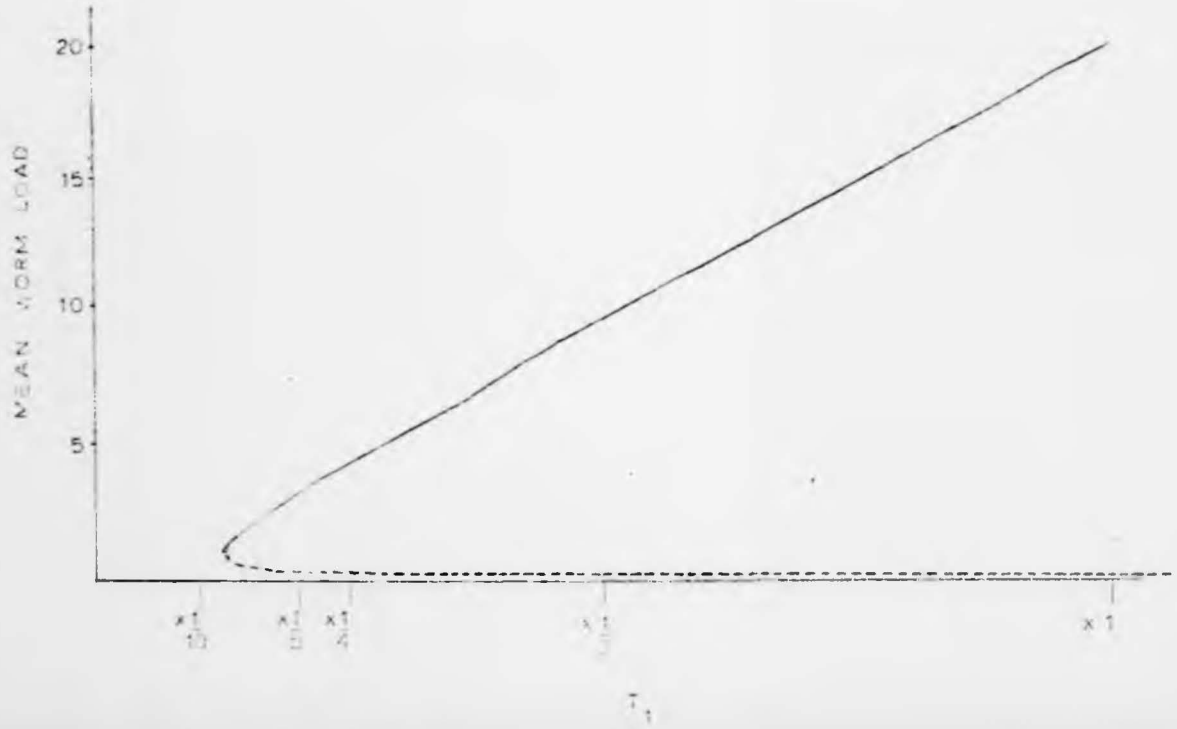
Graphical study of effects of clumping in the Macdonald model.

FIGURE II-6



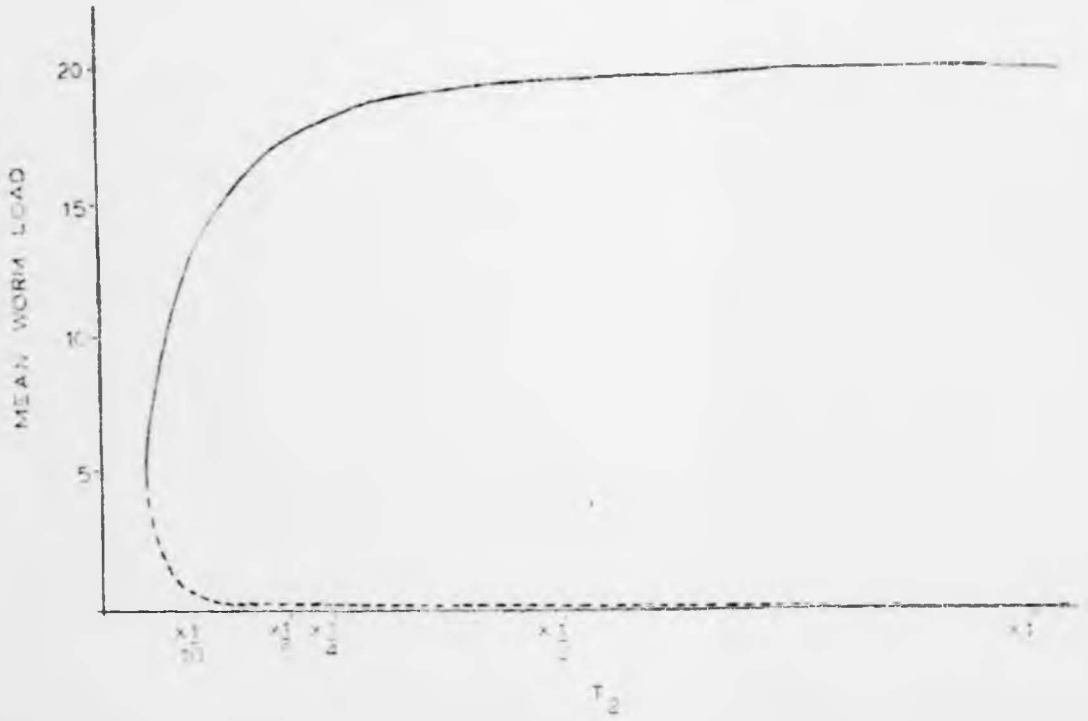
Sensitivity of equilibrium mean worn load to Wanell-Hirsch transmission factor T_1.

FIGURE II 7



Sensitivity of equilibrium mean worm load to Nasell-Hirsch transmission factor T_2.

FIGURE II-8



Phase space of dynamic relation between mean worm load and proportion of infected snails.

FIGURE II-9

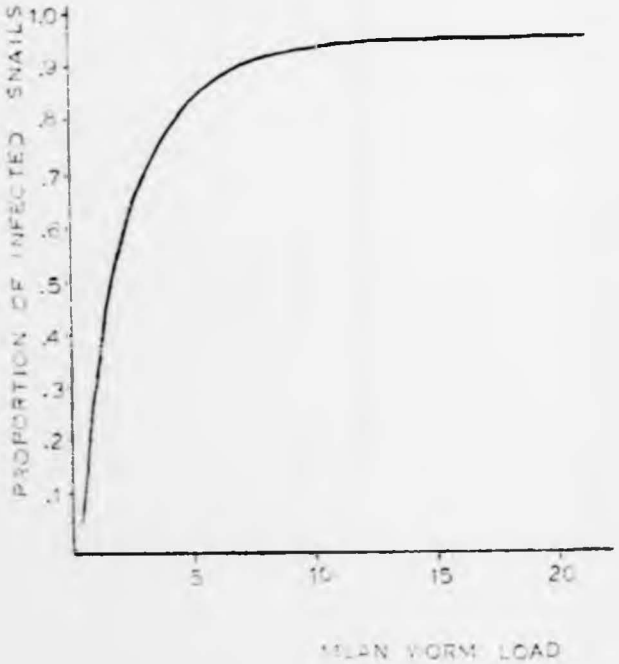


Table II-1

Input Values and Parameters Copied from Macdonald's Computer Listing.

Name	"Standard" Population	Macdonald's Parameter	Suspected Interpretation
Y_0	0.015	$(k_2z_2)E$	$(k_2z_2)E$
Y_1	1.25	$(k_1er)PE$	$(k_1z_1)EP/L$
Y_2	0.95	p	p
Y_3	0.001	r	r
Y_4	0.1	m(initial)	m(initial)
Y_5	25	n	n
Y_6	5	S	S

Table II-2

Macdonald's Factors, Parameters and Input Variables.

Factor	Parameter	Input Variable
Exposure	k_2	Y_0
Contamination	k_1	Y_1
Longevity	r	Y_3
Snails	S	Y_6

Table II-3

Values of Parameters in Macdonald's Model

Parameter	Value
P	1000
L	1000
z_1	1000
Ek_1	1.25×10^{-3}
S	5
p	.95
r	.001
n	25
k_2	.02
Ez_2	0.75

Table II-4

The effect of changing contamination on the equilibrium proportion of snails infected and patent.

Contamination factor	r=0.001		r=0.005	
	Infected	Patent	Infected	Patent
$x^1/_5$	.85	.23	-	-
x^1_2	.94	.26	.47	.13
x1	.97	.27	.78	.22
x2	.97	.27	.90	.25

Chapter Three:- Transmission Model with Age Dependent Exposure

It has been noted that empirical age-prevalence and age-intensity of infection curves are frequently unimodal, whereas the Macdonald-Nåsell-Hirsch (MNH) model predicts sigmoid curves. One immediate benefit then, of the modelling exercise to date is to note that at least another factor (if not more) needs to be incorporated in any "explanation" of the dynamics of transmission. A favoured consideration must be an allowance for immune response. While this phenomenon is not yet universally accepted, considerable biochemical evidence is accumulating. The purpose of the current model, however, is to study an alternative consideration, by investigating the extent to which the age-intensity of infection curve is changed by allowing for varying exposure by different age groups of the definitive host.

The model described below involves a particularly large number of parameters, and yet makes little change in the basic formulation of MNH. It is felt that the parameters introduced were much more amenable to estimation than those which are retained from the Macdonald-Nåsell-Hirsch formulation. Furthermore,difficulties of a theoretical nature in this model stem less from the introduction of many parameters, but more from the expansion into several age groups. In Chapters Four and Five, field data are used to study empirically the model's behaviour, and it is hoped that results are more realistic through use of these parameters.

1) Variables

The human population in a closed, homogenous ecological complex is assumed to be split into nine age groups, each bearing mean worm loads as

follows:

Age Group	Mean Worm Load per Human	Number of Human Hosts
0-4 yrs	$m_1(t)$	N_{11}
5-9 yrs	$m_2(t)$	N_{12}
10-14 yrs	$m_3(t)$	N_{13}
15-19 yrs	$m_4(t)$	N_{14}
20-29 yrs	$m_5(t)$	N_{15}
30-39 yrs	$m_6(t)$	N_{16}
40-49 yrs	$m_7(t)$	N_{17}
50-59 yrs	$m_8(t)$	N_{18}
60+ yrs	$m_9(t)$	N_{19}

The actual number of age groups is fixed at nine for present purposes to facilitate application of the model in subsequent sections. Alterations to different numbers is trivial. It is also assumed that the transmission of male and female schistosomes involving male and female definitive (and intermediate) hosts does not depend upon the sex of either the host or parasite.

The snail population is assumed to be split into three groups: the proportion uninfected $x(t)$, the proportion infected but not yet releasing cercariae (prepatent) $z(t)$, and the remaining proportion, infected and releasing cercariae (patent) and thus contributing to transmission $y(t)$.

The model therefore consists of twelve variables, but, with the restriction $x(t) + y(t) + z(t) = 1$, is in eleven dimensional space.

2) Parameters

N_{1_i}

The number of human hosts is assumed fixed. Values of N_{1_i} for various age groups are summarized above.

N_2

The number of snails is likewise assumed fixed.

λ_1

The "instantaneous" rate of shedding ova into the habitat by one paired female worm is given by λ_1 (eggs per paired female schistosome). For present purposes, it is convenient to think of "instantaneous" approximated by "daily". Thus λ_1 is the number of eggs released per paired female schistosome in one day.

p_2

The transmission of infection to an uninfected snail involves several steps. A released egg must reach the water and subsequently hatch. The miracidium must then locate and penetrate a snail. Only a fraction of those eggs released succeed in producing a new infection in a given snail. The probability one miracidium succeeds in infecting a given uninfected snail is p_2 (snail infections per egg). The product $\lambda_1 p_2$ symbolizes the number of new infections from a paired female schistosome. In realistic situations $\lambda_1 p_2$ will be less than one, representing the probability a paired female schistosome infects a given uninfected snail.

λ_2

The instantaneous (or daily) rate of shedding of cercariae from a patently infected snail is given by λ_2 (cercariae per patent snail).

p_{1_i}

Transmission of infection from snail to man, like that from man to snail involves several steps. Cercariae need to be released into water flowing under appropriate conditions, the human exposure to water needs to occur and the penetration and eventual production of a schistosome all need to occur. Only a fraction of the cercariae released succeed in completing these steps. In this formulation, the human exposure to water differs over the various age groups. The probability a cercaria successfully infects a given human in age group i is denoted by p_{1_i} (schistosomes per cercaria). The product $\lambda_2 p_{1_i}$ will (in realistic circumstances) be less than one and is interpreted as the probability a patent snail produces a new schistosome in a host in age group i.

μ_1

The daily death rate of schistosomes is assumed to be a constant, μ_1 (per day).

μ_2, μ_2' and μ_2''

The daily death rates of uninfected, infected prepatent and infected patent snails are assumed to be constant with rates μ_2, μ_2' and μ_2'' (per day) respectively.

τ

A fixed latency period of τ days is assumed.

The remaining parameters describe flows of worms into, out of, and between the human populations of each age group. A distinction is made between movements of worms between the community under consideration and areas outside this community, and movements of worms between age groups

within the community. The former is to model movements of (possibly infected) humans into and out of the village and the latter is to describe the effects of humans aging out of one age group into the next. Care must be exercised in differentiating between movement of worms (the flows of which the model describes) and those of humans (more readily observed, but not directly modelled here). This consideration will be discussed below.

ξ_i

The number of people who daily enter group i by aging from group i-1 is given by ξ_i (people per day). If the mean worm load of age group i-1 is $m_{i-1}(t)$ and ξ_i of these people enter group i daily, the gain in mean worm load in age group i is $\xi_i m_{i-1}(t)/N_{1_i}$.

η_i

To complement the gain from aging in group i, allowance must be made for loss in age group i-1. The number of people who are lost daily by aging from group i to i+1 is denoted by η_i (people per day). If the η_i people bear a mean worm load of $m_i(t)$ worms per person, then $\eta_i m_i(t)$ total worms are lost daily, and the effect is to decrease the mean worm load of group i by $\eta_i m_i(t)/N_{1_i}$.

Obviously the use of both ξ_i and η_i is unnecessary and it can be seen that $\eta_i = \xi_{i+1}$ for i = 1...8. As well, there is no aging into the first age group ($\xi_1 = 0$) or out of the last ($\eta_9 = 0$).

δ_i

Worms can be lost to the community through either the emigration or death of their human hosts. The number of humans lost to age group i per

day is denoted δ_i (people per day). If the δ_i people lost have a mean worm load of $m_i(t)$ then the mean worm load in age group i is decreased by $\delta_i m_i(t)/Nl_i$.

ε_i

The treatment of the immigration of worms into the community differs from that of η_i, ξ_i, and δ_i above. In these three situations it is not unreasonable to assume the humans which moved bore worm loads given by $m_i(t)$, which is predicted by the model. It is not thought reasonable to assume humans entering the community from outside bear the same mean worm load as those within the village. Fortunately there are situations where the infectivity of immigrating individuals is known. Thus, rather than determine the flow of people into the area from outside and calculate the influx of worms from this basis, it is assumed that ε_i worms daily immigrate to age group i. The effect is to increase the mean worm load in age group i by ε_i/Nl_i .

It would be possible to treat δ_i on the same basis as ε_i, as infectivity data may be available on lost humans. It is thought that to do so would reduce the theoretical and practical aspects of the model. To allow for the observed number of worms lost would produce a more empirical or life table formulation. As well, anyone seeking to implement such a model would possibly find it inconvenient to determine the infectivity of emigration or dying humans, and much more satisfactory merely to count the number of hosts lost.

It is important to note as well that allowance has been made in the above description for flows between the $m_i(t)$ while the Nl_i are assumed

fixed. It is possible that situations might arise in which there was immigration and emigration but the N_{1_i} remain constant. This is equivalent to the assumption made by keeping N_2 constant: loss of an infected or uninfected snail is compensated by an immediate replacement by a newborn uninfected one. In cases where there are slight changes in the N_{1_i} the effect of not considering them is minor in comparison with the effects of ignoring immigration and emigration of the worms themselves. Lewis (1975b) has proposed a model in which the human population variations are modelled.

3) System of Equations

In a time interval of Δt, the worm load in age group i increases due to immigrating worms and infection from contact with infected water. There are losses in mean worm loads through emigration and death of hosts, as well as deaths of the schistosomes themselves. The resultant total worm load is given by:

$$N_{1_i}m_i(t+\Delta t) = N_{1_i}m_i(t) + \lambda_2 p_{1_i} N_{1_i} N_2 y(t)\Delta t + \varepsilon_i \Delta t +$$

$$\xi_i m_{i-1}(t)\Delta t - \delta_i m_i(t)\Delta t - \eta_i m_i(t)\Delta t - \mu N_{1_i} m_i(t)\Delta t + o(\Delta t)$$

The changes in infection in the snail population are less straightforward. Of the $N_{1_i}m_i(t)$ worms in age group i, only a fraction are assumed paired, and half of those paired are assumed female. For present purposes, the proportion paired is denoted $\phi(m_i(t))$, where some fundamental properties of ϕ are:

$$\lim_{m \to 0_+} \phi(m) = 0$$

$$\sup_m \phi(m) \leq 1$$

$$\frac{d\phi(m)}{dm} \geq 0 \text{ for } m \geq 0 \quad .$$

Further specifics of $\phi(m)$ are deferred until the next chapter, where the work by May (1977) on such functions is mentioned.

The change of infection in prepatent snails involves increase from infected definitive hosts and losses through death and transition to patency.

As N_2 is assumed fixed, loss of snails from any category is conceptualized as death followed by instant replacement by an uninfected snail. (This is essentially a steady state assumption amongst the snail numbers.)

It is convenient to denote by $h(t)$ the chances a given snail is infected by the infected individuals in the area considered

$$h(t) = \tfrac{1}{2} p_2 \lambda_1 \sum_{i=1}^{9} N_{1_i} m_i(t) \phi(m_i(t)) \quad .$$

The losses from the prepatent snail population to patency incorporate a "lag feature". May (1977) describes such models in the Macdonald-Nåsell-Hirsch setting, and notation herein is kept as similar to his as possible. The number of prepatent snails lost to patency is taken as the number infected τ days ago, when corrected for survival of the τ days (by $e^{-\tau u_2'}$). Thus:

$$N_2z(t+\Delta t) = N_2z(t) + h(t)N_2x(t)\Delta t - e^{-\mu_2'\tau}h(t-\tau)N_2x(t-\tau)\Delta t - \mu_2'N_2z(t)\Delta t + o(\Delta t)$$

The number of patent snails after Δt is:

$$N_2y(t+\Delta t) = N_2y(t) + e^{-\mu_2'\tau}h(t-\tau)N_2x(t-\tau)\Delta t - \mu_2''N_2y(t)\Delta t + o(\Delta t)$$

Writing

$$m_i \equiv m_i(t)$$

$$x \equiv x(t) \text{ and } x^{\dagger} = x(t-\tau)$$

$$y \equiv y(t)$$

$$z \equiv z(t)$$

$$h \equiv h(t) \text{ and } h^{\dagger} = h(t-\tau)$$

and letting:

$$\frac{dm_i}{dt} = \lim_{\Delta t \to 0} \frac{m_i(t+\Delta t) - m_i(t)}{\Delta t}$$

the system of equations modelling the flow of infection follows:

$$\frac{dm_1}{dt} = \lambda_2 p_{11} N_2 y + \frac{\varepsilon_1}{N_{11}} - (\mu_1 + \frac{\delta 1 + \eta_1}{N_{11}})m_1 \qquad \text{(III - 1)}$$

$$\frac{dm_2}{dt} = \lambda_2 p_{12} N_2 y + (\frac{\varepsilon_2 + \eta_1 m_1}{N_{12}}) - (\mu_1 + \frac{\delta 2 + \eta 2}{N_{12}})m_2 \qquad \text{(III - 2)}$$

$$\frac{dm_3}{dt} = \lambda_2 p_{13} N_2 y + (\frac{\varepsilon_3 + \eta_2 m_2}{N_{13}}) - (\mu_1 + \frac{\delta_3 + \eta_3}{N_{13}})m_3 \qquad \text{(III - 3)}$$

$$\frac{dm_4}{dt} = \lambda_2 p_{14} N_2 y + (\frac{\varepsilon_4 + \eta_3 m_3}{N_{14}}) - (\mu_1 + \frac{\delta_4 + \eta_4}{N_{14}})m_4 \qquad \text{(III - 4)}$$

$$\frac{dm_5}{dt} = \lambda_2 p_{15} N_2 y + (\frac{\varepsilon_5 + \eta_4 m_4}{N_{15}}) - (\mu_1 + \frac{\delta_5 + \eta_5}{N_{15}})m_5 \qquad \text{(III - 5)}$$

$$\frac{dm_6}{dt} = \lambda_2 p_{16} N_2 y + (\frac{\varepsilon_6 + \eta_5 m_5}{N_{16}}) - (\mu_1 + \frac{\delta_6 + \eta_6}{N_{16}})m_6 \qquad \text{(III - 6)}$$

$$\frac{dm_7}{dt} = \lambda_2 p_{17} N_2 y + \left(\frac{\varepsilon_7 + \eta_6 m_6}{N_{17}}\right) - \left(\mu_1 + \frac{\delta_7 + \eta_7}{N_{17}}\right) m_7 \qquad \text{(III - 7)}$$

$$\frac{dm_8}{dt} = \lambda_2 p_{18} N_2 y + \left(\frac{\varepsilon_8 + \eta_7 m_7}{N_{18}}\right) - \left(\mu_1 + \frac{\delta_8 + \eta_8}{N_{18}}\right) m_8 \qquad \text{(III - 8)}$$

$$\frac{dm_9}{dt} = \lambda_2 p_{19} N_2 y + \left(\frac{\varepsilon_9 + \eta_8 m_8}{N_{19}}\right) - \left(\mu_1 + \frac{\delta_9}{N_{19}}\right) m_9 \qquad \text{(III - 9)}$$

$$\frac{dz}{dt} = hx - e^{-\mu_2' \tau_h^{\dagger}} x^{\dagger} - \mu_2' z \qquad \text{(III - 10)}$$

$$\frac{dy}{dt} = e^{-\mu_2' \tau_h^{\dagger}} x^{\dagger} - \mu_2'' y \ . \qquad \text{(III - 11)}$$

4) Asymptotic Theory

Conditions are now considered under which various equilibrium states can exist.

The first nine equations form a linear system which, for a given value of y, will produce a unique set of equilibrium mean worm loads (with $dm_i/dt = 0$ for all $i = 1, \ldots, 9$). Considering the total number of paired worms in the equilibrium situation ($W_a^* \equiv \sum N_{1i} m_i^* \phi(m_i^*)$) one notes that this is a function of y where $m_i^* = a_i y + b_i$, with $a_i, b_i \geq 0$ for $i = 1, \ldots, 9$. (Below, another equation involves the total number of paired worms W, and the subscript a is introduced here to differentiate from the later use of W. Generally, the asterisk superscript denotes a variable or function of variables with asymptotic values.) Writing:

$$\begin{aligned} W_a^* &\equiv \sum_{i=1}^{9} N_{1i} m_i^* \phi(m_i^*) \\ &= \sum_{i=1}^{9} N_{1i} (a_i y + b_i) \phi(a_i y + b_i) \\ &= y \left(\sum_{i=1}^{9} N_{1i} a_i \phi(a_i y + b_i) \right) + \sum_{i=1}^{9} N_{1i} b_i \phi(a_i y + b_i) \end{aligned} \qquad \text{(III - 12)}$$

One has

$$\frac{dW_a^*}{dy} = y \sum_{i=1}^{9} N_{1i} a_i^2 \frac{d\phi_i(m_i)}{dm_i^*} + \sum_{i=1}^{9} N_{1i} a_i \phi(m_i) + \sum_{i=1}^{9} N_{1i} b_i \frac{d\phi_i(m_i)}{dm_i}$$

$$\frac{dW_a^*}{dy} \geq 0 \text{ for } y \geq 0.$$

Assuming $W_a^*(y)$ is continuous for $y \in [0,1]$, there is a unique value of W_a^* for each $y \in [0,1]$.

Consider now a three dimensional space involving the total number of paired worms, the values of z, and those of y. Values of the m_i^* as a function of y produce a curve of the (W,y) space which is independent of the values of z, thus yielding a unique sheet in the (z,y,W) space along which the first nine equations satisfy $dm_i/dt = 0$.

With $x^+ = x$ and $h^+ = h$ in the equilibrium situation, equation (III-10) can be rewritten as:

$$h^*(1 - e^{-\mu_2'\tau})x^* - \mu_2' z^* = 0$$

when $dz/dt = 0$. As $x^* + y^* + z^* = 1$, one has

$$h^*(1 - e^{-\mu_2'\tau})(1 - y^* - z^*) - \mu_2' z^* = 0 \qquad \text{(III - 13)}$$

and as $h^* = cW^*$ with $c = \frac{1}{2}\lambda_1 p_2$ then

$$W^* = \frac{\mu_2'}{c(1 - e^{-\mu_2'\tau})} \times \frac{z^*}{(1 - y^* - z^*)} \qquad \text{(III - 14)}$$

Equation (III-14) describes a series of hyperbolae in the (W,z) space. All hyperbolae share the point (0,0) and the asymptote is a linear function of y^*: $z_{asym} = 1 - y^*$. In three dimensional space, equation (III-14) resembles a trough along the z axis, widest at $y = 0$ and narrowing to a slit at $y = 1$. At $y = 1$, equation (III-13) describes a line, as h can be any value.

Considerations for the last equilibrium equation:

$$e^{-\mu_2'\tau} h^*(1 - z^* - y^*) - \mu_2' y^* = 0 \qquad \text{(III - 15)}$$

$$\text{or} \quad W^* = \frac{\mu_2''}{ce^{-\mu_2'\tau}} \frac{y^*}{(1 - z^* - y^*)}$$

are essentially the same, except the "trough" lies along the y axis, and the constant multiplier for each hyperbola ($\mu_2''/ce^{-\mu_2'\tau}$) differs from that previous ($\mu_2'/c(1 - e^{-\mu_2'\tau})$).

The intersection of the above two sheets, satisfying equilibrium equations (III-13) and (III-15) produces the relation between y and W_b^*:

$$W_b^* = \frac{\mu_2' \mu_2'' y^*}{c\mu_2' e^{-\mu_2'\tau} - c\{\mu_2''(1 - e^{-\mu_2'\tau}) + \mu_2' e^{-\mu_2'\tau}\} y^*} \qquad \text{(III - 16)}$$

which is itself a hyperbola with an asymptote at:

$$y^*_{lim} = \frac{\mu_2' e^{-\mu_2'\tau}}{\mu_2' e^{-\mu_2'\tau} + \mu_2''(1 - e^{-\mu_2'\tau})} \quad . \qquad \text{(III - 17)}$$

One has thus a means of studying the existence of equilibrium states for any set of parameter values. This is analogous to the technique described with Macdonald's 1965a model in Chapter Two, and involves studying the intersection of two lines.

Whereas the fashion has been to study the behaviour of various models using mean worm load as the prime index of interest, an alternative is employed here. Although it is feasible to study the effects on the number of worms or the number of paired worms (W), it is as easy to study behaviour of the system as a function of the proportion of patently infected snails (y). It matters very little which variable is studied,

and whereas most models betray their invalidity when the predicted values of y are studied, by using y as the basis for study, one is constantly alert to the possibly weakest aspect of the model.

In this case, the two lines to be studied relate W^*(or h^*) and y^*, and the relationships are given by equations (III-12) and (III-16). Plotting W^* vertically and y^* horizontally, the complicated curve given by (III-12) divides the (y,W) space into two regions. All points in the region above the line are associated with $dW_a/dt < 0$ and those below $dW_a/dt > 0$. Similarly, the hyperbola described by (III-16) divides the (y,W) space into points to the right (for which $dy/dt < 0$) and left (with $dy/dt > 0$). Along the lines, the corresponding derivatives are zero, and at the intersections of the two lines, one has the equilibrium situations.

Three situations are possible, depicted by Figure III-1. There is some, but not complete, correspondence to Macdonald's situations, displayed in Figure II-3. The number and nature of critical points in these cases have been rigorously explored by Näsell (1975, especially Theorem 6.1). Herein an intuitive approach is followed. In the first case (a), three intersections are noted at values of y: y_ℓ, y_b and y_h. The point at y_ℓ is a lower stable critical point in which infection is solely due to immigration of worms, and not through transmission within the community. The value of y_b is Macdonald's "breakpoint", an unstable critical point. A system with a proportion of patently infected snails greater than y_b will eventually settle at the higher equilibrium value, y_h, while a system with y less than y_b will settle at the lower value y_ℓ. It is theoretically possible, but unlikely, that a situation can occur

in which y is exactly at y_b and is not disturbed. Any disturbance would lead to the value of y_ℓ or y_h eventually being reached.

The possibility of situation (b) of Figure III-1 occurring is unlikely as well. To go from situation (a) to (b) parameters are altered either raising curve W_b^* or lowering curve W_a^*. As this happens points y_b and y_h in situation (a) converge to point y_c in situation (b) where the curves just touch. The value of y_c is an unstable equilibrium and any perturbation producing a y less than y_c will result in an eventual value of y_ℓ.

In the last situation, (c), the two lines cross only once, and it is instructive to possibly consider two sub-cases of this (although one cannot readily distinguish between the two in practice). Where the lines cross yielding a low value of y_d, one might conclude, as for y_ℓ above, that any infection in the community is due to the immigration of infection, and not through internal transmission. This was described in Chapter Two as the "washout" of the breakpoint.

If, however, the unique crossing occurs at a higher level, then another phenomenon may be occurring. In Figure III-1, situation (a), the existence of y_ℓ and y_b (indeed, the breakpoint phenomenon) can be traced to the peculiar behaviour of equation (III-12) for low values of y. Macdonald correctly noted that pairing has a dramatic effect on transmission, particularly at low infection levels. The effect of immigration on equation (III-12) has been to displace the W_a^* intercept above the point (0,0), and this, with an appropriate selection of other parameters, may preclude the intersection of the two lines which gives rise to the two critical points y_ℓ and y_b. In this situation, the

effect of pairing is minimized, and one is conceptually in an asexual situation. This is another form of "washout" of the breakpoint. In the previous case, the "washout" was associated with low levels of infection in which transmission was not possible. In this case, the "washout" produces the only intersection at a high level of infection, and any hope of reducing infection (and keeping parameters similar) by reaching a level below a breakpoint is incorrect.

The nature and number of equilibrium points can be determined graphically, as described above. While non-linearities, especially in equation (III-12), make algebraic solutions impossible, a numerical approach is described below. There is always one point where equations (III-12) and (III-16) cross. The hyperbola given by (III-16) increases monotonically from 0 to infinity as y varies from 0 to y^*_{lim} given by (III-17). If (0,0) is a solution for (III-12), then this is a stable, critical point. Alternatively, as $W_a^*(y=0) > 0$, and as $W_a^*(y=1) < \infty$, then the lines described by the two equations must cross at least once.

An algorithm follows to determine if there are three critical points rather than one. Between 0 and y_{lim} the function $g(y) = {}^{dW_a}/_{dy} - {}^{dW_b}/_{dy}$ is unimodal with an asymptote at y_{lim}. If $g(0) \geq 0$, as $W_a(0) \geq 0$, there is only one intersection of $W_a(y)$ and $W_b(y)$. (This is evidence that the pairing effects are minimal and no low breakpoint exists.) When $g(0) < 0$, the values y_1 and y_2 are found where $g(y_i) = 0$, $i = 1,2$ and $0 < y_1 < y_m < y_2$ with

$$y_m = \sup_{0 < y < y_{lim}} g(y).$$

Letting $f(y) = W_a(y) - W_b(y)$, only one intersection of $W_a(y)$ and $W_b(y)$ exists if $f(y_1) > 0$ or $f(y_2) < 0$. If neither of these conditions is met, search methods are used to find y_ℓ, y_b and y_h where $f(y) = 0$ and $0 \leq y_\ell \leq y_1 \leq y_b \leq y_2 \leq y_h \leq y^*_{lim}$.

Solution of the system of equations (III-1) to (III-11) is straightforward once an equilibrium value of y^* is established. Individual mean worm loads are most easily obtained recursively from:

$$m_1^* = \frac{1}{k_1} \{\lambda_2 N_2 p_{11} y^* + \frac{\epsilon_1}{N_{11}}\}$$

and

$$m_i^* = \frac{1}{k_i} \{\lambda_2 N_2 p_{1_i} y^* + \frac{\epsilon_i}{N_{1_i}} + \frac{\eta_{i-1}}{N_{1_i}} m^*_{i-1}\} \quad \text{for } i = 2,\ldots,9.$$

with $$k_i = \mu_1 + \frac{\delta_i}{N_{1_i}} + \frac{\eta_i}{N_{1_i}} \qquad i = 1, \ldots, 9$$

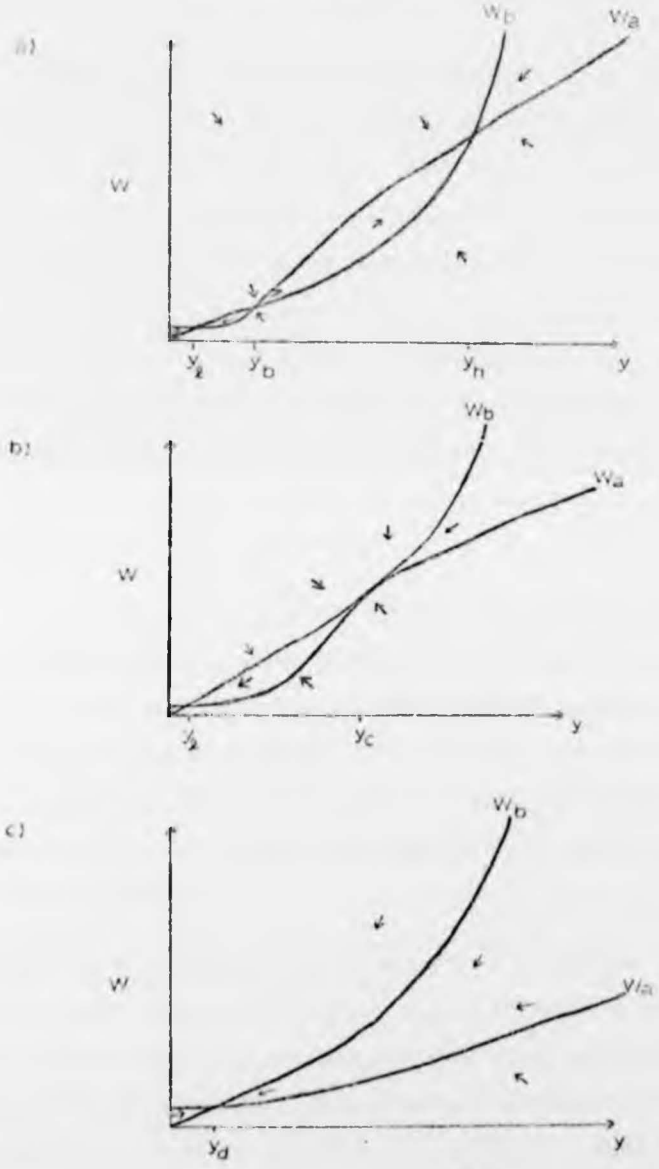
and $$\eta_9 = 0.$$

Once obtained, the values of m_i^* can be used to calculate W^* and hence h^*, which with y^* can be used with equation (III-10) (by setting the right-hand side equal to zero) to obtain the equilibrium proportion of infected, prepatent snails, i.e.:

$$z^* = \frac{h^*(1 - e^{-\mu_2'\tau})(1 - y^*)}{h^*(1 - e^{-\mu_2'\tau}) + \mu_2'} \quad .$$

Graphical study of economic model. Three possible situations with three (a), two (b) and one (c) critical points.

FIGURE III-1



Chapter Four:- Estimation of Variables and Parameters

The two authors who pioneered the development of mathematical studies of the entire transmission cycle of schistosomiasis (Macdonald in 1965a, Hairston in 1962 and 1965) both chose values for variables and parameters, and studied the behaviour of each model under particular parameterizations. Such an approach can be criticized in that one is only studying a model's behaviour restricted to a subset of all possible values, and analytic study alone can establish the full generality of the properties of a certain formulation. On the other hand, some hold that development of theoretical mathematical models which provide satisfying general attributes may be sacrificing detail obtainable within parameter sets of interest.

In the series of articles by several authors subsequent to these initial works, few (for example Huffman, 1972) seem to have attempted the task of substituting values in models for the complete cycle. Work by Nåsell (1977 etc.) and Nåsell and Hirsch has been dominated by theory. Alternatively, when models have been developed and studied with real data, they have tended to be on specific sections of the cycle (Holford (1973) and Rosenfield (1975)).

Thus, it seems appropriate to attempt an estimation of parameter values to study the behaviour of the model developed in Chapter Three. After a brief introduction to the area from which estimates were obtained, mention will be made of how values for the variables, mean worm counts and proportions of snails infected, are obtained. Following this, a description will be given as to how each parameter mentioned in Chapter

Three is obtained.

1) Area Under Study

In the mid sixties, the Rockefeller Foundation started a research project, under the directorship of Dr Peter Jordan, to study the control of Schistosomiasis mansoni on the West Indian island of St Lucia. One of the first technical advisors to this project was Professor Macdonald, and it was hoped that the St Lucia experiment would, as one of many aims, provide a means of studying his model's predictions. After several years of studies to measure the spread of disease and possible factors, carefully planned "control" measures were begun and their effects on the disease were studied. Despite the size of the project and the long time it has been running, it is becoming known for the scrupulous care that has gone into every facet of the process, including the careful maintenance of records. Most of the published work to date has been from concomitant biological, medical and other studies (for example, Upatham (1976), Sturrock (1973), Prentice et al (1976) and Cook (1976)). While some epidemiological studies have been published (Jordan (1975), Unrau (1975)), the majority of results are kept as annual reports to the Rockefeller Foundation, possibly for future use to compare the various control strategies. Jordan (1977) has recently discussed some of the broader results from the St Lucia studies.

The data from which the values used in the model are obtained come from an area of St Lucia near the head of the Cul de Sac valley called Ravine Poisson, within the area Bexon. Whereas the majority of the entire valley was given to banana production, during the years considered

here, this particular region was not. The Cul de Sac river lies between steep hillsides in this residential area and there is little room for banana cultivation. Houses lie either alongside the river and tributaries, or around marshes that drain into the river. The inhabitants are exposed to infected water mostly through the activities of washing, playing, bathing, carrying water and fording. Contamination takes place with the emptying of chamberpots in or near the marshes and rivers. The area specifically considered here is about 0.7kms long and varies in width from about 100 to 250 metres. Figure IV-1 presents a sketch of the area. The wettest months are from July to December and the average monthly rainfall is 25 centimetres during this wet season, and 13 centimetres during the dry period. Mean monthly temperatures vary from 23°C in January and February to 28°C in July and August.

The particular parts of Ravine Poisson chosen (coded as sites X, Y and Z and YZ by the Research and Control Department) were studied from the project's instigation for several years until, in 1970, a molluscicide campaign was begun. The inhabitants were counted and periodically studied for presence of schistosome eggs in stools. The marshes, rivers and ponds were studied for presence of snails, and the level of infectivity of those snails found was determined. In addition, the infectivity of the water was studied by means of sentinel mice and sentinal snails. On occasion, cercariometric methods were also used.

Within the overall area there are six sub areas. These are identified by the codes NX, X, RB, Agric, YZ and SYZ, which represent a river section North of X, fed by the marsh X itself, a River Bank flowing into X and three streams Agric, YZ and SYZ flowing into the river. Sub area YZ was originally a marsh Y and river Z, which were later

amalgamated. The stream SYZ (South of YZ) is really the same river that feeds into marsh X farther below. It is noted in passing that the flow of disease is not wholly cyclic within these sub areas. For example, people around X not only contribute to their own infections, but also possibly recieve cercariae from the River Bank sub area and contribute to NX infections. Figure IV-2 sketches possible flows of infection. Sadly, the model considered here is not adapted to allow for such flows between sub areas. It is felt that the current model is sufficiently complicated for current purposes and warrants study before adaptations along the lines mentioned above are embarked upon. All the data is thus considered to represent one homogenous whole, in that by pooling various quantities, differences are "averaged out". Table IV-1 summarizes the six sub areas along with the Research and Control household numbers associated with each. The area of marsh or length of riverbank is noted as well.

Although any estimates of parameters for models attempting to summarize the entire cycle will be very crude at this stage of development, this particular area may provide as good values as can currently be provided.

2) Snail Numbers and Infection Rates

As both infected proportions (y) and snail numbers(N_2) were determined together in the field, this variable and parameter are best considered together. Surveys for snails were performed approximately fortnightly from February 27, 1967 in sub areas X,Y, and Z (later X and YZ). These continued until the summer of 1970 when marsh X was drained and, with the

rest of Cul de Sac valley, a molluscicide campaign was begun following which no snails were found. From these biweekly results, for 1967 to 1970, a standing crop of total snails is estimated, and an average number of infected snails has been calculated. Sampled snails were placed in containers for a fixed time (about one hour) and the water was checked afterwards for evidence of cercariae. Thus, the infected snails represent patent infections only. Table IV-2 summarizes the average snail counts, infected snail counts and infected proportions. It is seen that site X particularly exhibits considerable variation and all sites display very low overall infection rates in snails. In light of this, the assumption in the model that the number of snails (N_2) is constant over the period of study is cast in doubt. Recourse is again made to the expedience of pooling values and hoping for an "averaging" of results. It is clear that, in future, models should consider the variation in snail population over time as well. (The model by Lewis (1975b)goes some way in this direction.)

From survey results, values for the entire area are obtained by simple mulitplication. In marsh X, the area sampled was 100 square feet (9.3 sq.metres) and quantities are then scaled up to the entire area of 0.5 acre (2025 sq.meters) with multiplication by 218. In each survey of marsh Z, four one-meter quadrats were used and the appropriate multiplying factor chosen is 1513. The only river surveyed was Z, and its results were deemed representative of rivers NX, Agric and SYZ. The Research and Control team studied the riverbank sub area and have never found snails. Multiplying factors based on comparative lengths have been used to predict overall populations for the area. (For example, NX is 500 meters long, Z is 50 meters and entirely sampled.

Therefore, NX's contribution is 500/50 = 10 times Z's contribution.)

Table IV-3 presents the annual overall estimated numbers of snails (N_2) and proportions which are patently infected.

3) Human Numbers and Intensity of Infection

With the exception of 1968, since 1967 there have been annual surveys of the people in the Ravine Poisson area. Not all people were studied every year, but records have been carefully kept on individuals for each time a stool count was made. When a sample was collected, it was first studied for the presence of eggs by means of a sedimentation technique. Stools without eggs were deemed negative, and no further examination was made. Those stools which showed eggs by this procedure underwent (where sufficient stool remained) a quantitative assessment (Bell, 1963) to determine the egg load per gram stool.

The main body of data on human infections is drawn from records held on 586 individuals, assumed to comprise all people who contributed to infection regularly during at least one survey period between 1967 and 1977. (That is, the records are not only of people resident in the area throughout the entire time, but contain immigrants and emigrants.) There is no information on short period transients, and it is hoped that they contributed little to the resident population's pool of infection.

The household number and sex of each person was noted and, for each survey record, there was included the age, diagnostic result (intensity of infection) and a "status" code. The latter feature indicated whether the individual was or was not infected and whether or

not treatment was administered. It was also used to indicate various categories of missing results. The status indicator in one year (say, for example, 1972) was used to note whether a person died or emigrated the previous year (1971), or was to be born or immigrate the following year (1973). In either case, there was no egg count, and one could rapidly tally up, for any intermediate year (1969 to 1976), the numbers of individuals and their egg counts gained or lost for various reasons. A person emigrating from the area in 1971 had the movement noted in 1972 only, and received a missing value from the area code from then on (1973 to 1977). Another missing code was given to individuals known to be in the valley, but for whom no observation was recorded. It was important to keep this particular form of missing value separate from others as such individuals were still contributing to transmission while all other "missings" were not. Lastly, a special code for people who emigrated in one year (say, 1971) and returned after a one year absence (1973) covered the remaining possibility. When allowance for changes in age group is made, one can study the movements of individuals in and out of the population which contribute to transmission. This is shown in Table A-1 in the Appendix.

With gains and losses each year in the human population, an estimate of the average yearly population was made. This was done by following the demographic practice of taking the survey value and incrementing by half the losses and decrementing by half the gains. (Spiegelman, 1968). The resultant values of N_{1_i} (i=1,...,9) are shown in Table A1 as well.

Whereas obtaining values for the parameters N_{1_i} involves few

serious assumptions, such is not the case in obtaining values for the variables m_i. Two general stages of obtaining this are described. Firstly, the mean egg burden in the population is obtained, then secondly, this must be related to the mean worm burden.

The first stage involves some form of missing value technique to provide values for individuals possibly contributing to transmission in the area during a given period, but for whom no stool examinations were performed. As this concerns the quantitative test results, there are also two other sources of missing observations. On some occasions, after being assessed as infected qualitatively, there was insufficient stool to perform a quantitative test. This happened in 72 of the 5860 observations. As well, some people were treated for the disease (especially in 1975 and 1976) and the pre-treatment egg count was not given. This happened 39 times.

Missing values are substituted as follows. For those missing between two observed values, a value is produced by simple linear interpolation. When a missing value is flanked by only one observation, that value is substituted. This approach can be particularly hazardous as it is tantamount to assuming that a steady state exists for such an individual. It makes no allowance for death of worms (with a value of $r = 0.001$ used below, in one year $e^{-365 \times .001} = .69$ of the schistosome population will die) or for uptake of worms. It is thought that other weaknesses in the model (such as the treatment of snails) preclude an elaborate adjustment for this factor, and this expedient will suffice the purpose at hand. Treated individuals are given the pretreatment egg count, or its estimate (mentioned below) for the current year, but have

a value of 0 if estimation was needed in the years following (exclusively 1976 and 1977).

On some occasions, people were known to be in the area for one or several years, but no stool results were obtained. For these people, the mean egg load over all non-missing people in the same age group for that year has been substituted. Qualitatively positive people with missing quantitative results were assigned the mean egg load of all infected known cases in the same age group for the year. (It was thought that knowing people were infected and substituting simple overall means would underestimate the mean egg load.) In all cases, the arithmetic and not the geometric mean is used. Some individuals were judged to be infected by qualitative means, but a quantitative test produced a null result. The minimum detectable count of the procedure employed is ten eggs per gram, and this value has been substituted for the zero.

In summary, two passes were made in estimating the egg burdens. During the first, linear interpolations or substitutions based on most recent non-missing value are used on an individual basis. On the second pass, missing values are replaced by the average egg count for the particular age group and year. For those cases known infected but with a missing count, the mean of infected people was substituted. It is worthwhile noting that this predictive procedure is used purely to estimate what a total population intensity of infection may have been. The resultant figures are specific to the modelling exercise at hand and should not be used in comparison with sampled values from other areas. It is hoped that by this means a better estimate of total infection for

this model is obtained.

Egg counts for all people in the valley at any given year thus obtained, the next stage involves estimating the mean worm loads in the population. This itself has two stages: a conversion from egg counts to worm pairs, and a calculation of unpaired worms from worm pairs. The former is best dealt with here, whereas the latter is better deferred until after a discussion of the pairing parameter estimates.

The relation between the worm pair load in a host and the amount of eggs found in faeces samples is a topic of considerable uncertainty. Even if there is a well defined relation between these quantities, the process of routine sampling is bound to obscure it greatly. For a given sample, one might consider sources of variation to include changes in oviposition during or between days, and sampling errors from the stool suspension. When dealing with village figures, variations between people need to be considered as well.

Hairston (1962) studied this relation in an interesting way. The population worm load was related to an estimated incidence figure within age groups. When this was related to the egg output, Hairston concluded that egg production per worm pair is not independent of the worm pair load. He allowed for this non-linearity in his lifetable form of model. Macdonald (1965a) and subsequently Nåsell and Hirsch (1973) assumed, as is done here, a linear relationship.

Each paired female is assumed to produce daily 250 eggs. This figure is from Jordan (personal communication). Of these, only 65% are here assumed to reach the faeces. The portion of viable ova retained in the tissues has attracted considerable attention. This figure is derived

from Cheever's (1968) Table 12 (p.52). For the five age groups studied, the proportion of eggs in the faeces (of those in liver and faeces) is .61, .61, .64,.65, .81 with a median of 0.64 and mean of 0.66. When the five age groups are combined, the (weighted) average percentage of eggs in the faeces is 65.3%. While it is unclear exactly what figure Macdonald may have had in mind for his formulation, Hairston (1965) employed a value of 0.303 (page 57 referring to page 56) for Schistosoma mansoni.

Egg counts are expressed per gram of faeces. To obtain the daily egg output, the mean value needs to be multiplied by the daily amount of faecal deposition. In an unpublished study, the eggloads and faeces weights of twelve patients in the St Lucia clinic were studied for a period of between sixteen and twenty-four days. The mean weights were not different over all individuals, regardless of age and sex, and the average weight was 123.76 grams (standard error of mean = 7.7 grams). This finding was in agreement with other published data: a paper by Pimparkar et al (1961) reported a mean weight of 115 grams (standard error of mean = 9.6 grams). The higher mean for St Lucians possibly reflects the larger fibre intake, but the values are not inconsistent.

The number of worm pairs is obtained from the observed egg loads (per gram faeces) by multiplication by 124 (grams per day) / (0.65 x 250 (eggs per paired female)) = .763. Egg loads of 0 were taken to indicate 0 worm pairs, values between 0 and $1/.763$ indicated 1 worm pair, between $1/.763$ and $2/.763$ indicated two and so on. The resultant worm pair counts are summarized in Table A-2 in the Appendix.

4) Pairing Parameters

Macdonald noted that the bisexual nature of schistosomes greatly altered the dynamics of transmission of schistosomiasis when compared to transmission of malaria. The distribution of worm pairs is strongly related to that of the worms themselves, and thus both distributions are important in the study of transmission. Macdonald chose to assume that worms were distributed among hosts according to a Poisson distribution, and derived the proportion of worms paired as a function of mean worm load (see Chapter Two). Nåsell and Hirsch (1973) showed that this distribution is an expected consequence of their formulation of Macdonald's model.

Spurred by the work of Crofton (1971), investigations have recently been made into the effect of relaxing this assumption. The main thrust of this work has been to explore the effects of "clumping" on the dynamics by May (1977). While such distributions cannot be rigorously linked to a stochastic mathematical basis (as the Poisson case can be), they are employed here as a pragmatic measure which will hopefully provide a more suitable model.

As the Poisson distribution for worms in hosts is the "parent" distribution in Macdonald's work, then the negative binomial is the parent in May's formulations (which will be employed here). Where m represents the mean worm load and k the "clumping factor" associated with the negative binomial situation, two alternative models are employed. The "together" situation assumes that the distribution of worms in hosts is given by a negative binomial distribution, and that a given worm in a host has a fifty percent chance of being one particular sex. The alternative, "separate" situation, assumes that male worms and female worms follow

separate negative binomial distributions and are distributed in hosts separately.

Writing the probability a host has n parasites as:

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

$$\text{where } \alpha = \frac{m}{m+k}$$

in the "together" situation, the probability of i males and j females is given by

$$P_t(i,j|m,k) = (1-\alpha)^k \frac{\Gamma(i+j+k)}{\Gamma(k)} \frac{(\alpha/2)^{i+j}}{i!j!}$$

where $\Gamma(k)$ is the real valued Gamma function.

The corresponding joint density in the "separate" situation is given by May as:

$$P_s(i,j|m,k) = (1-\alpha')^{2k} \frac{\Gamma(i+k)\Gamma(j+k)}{\Gamma(k)\Gamma(k)i!j!} (\alpha')^{i+j}$$

$$\text{where } \alpha' = \frac{m}{m+2k} .$$

The joint density using Macdonald's approach is:

$$P_m(i,j|m) = \frac{e^{-m}}{i!j!} \left(\frac{m}{2}\right)^{i+j} .$$

This can be derived either from heuristic arguments as discussed by May, or by evaluating

$$\lim_{k\to\infty} P_t(i,j|m,k) \quad \text{or} \quad \lim_{k\to\infty} P_s(i,j|m,k) .$$

(The approach using limits parallels the demonstration that a binomial distribution converges to a Poisson distribution as the sample space increases.)

From these densities, the distributions of pairs can be obtained. May shows the pair density function in the "together" situation to be:

$$\Pi_t(j \text{ pairs}|m,k) = \frac{(1-\alpha)^k}{j!j!} \frac{\Gamma(k+2j)}{\Gamma(k)} \left(\frac{\alpha}{2}\right)^{2j} \{2F(k+2j,1;j+1;\tfrac{\alpha}{2}) - 1\} \quad \text{(IV-1)}$$

where $F(a,b;c;z)$ is Gauss's hypergeometric function. (See Abramowitz and Stegun (1965), Chapter 15.) A similar expression for the separate case can be found:

$$\Pi_s(j \text{ pairs}|m,k) = \left[\frac{(1-\alpha')^k(\alpha')^j\Gamma(j+k)}{\Gamma(k)j!}\right]^2 \{2F(j+k,1;j+1;\alpha') - 1\}. \quad \text{(IV-2)}$$

The corresponding density in the Macdonald model is less concise:

$$\Pi_m(j \text{ pairs}|m) = \frac{e^{-m}}{j!} \left(\frac{m}{2}\right)^j \{2[e^{m/2} - \sum_{i=0}^{j-1} \frac{1}{i!} \left(\frac{m}{2}\right)^i] - \left(\frac{m}{2}\right)^j \frac{1}{j!}\}.$$

(As in obtaining $P_m(i,j|m)$, Π_m can either be obtained from P_m or by determining the limit as k increases of equations IV-1 or IV-2.)

The functions giving the proportion of worms paired, in a population of hosts bearing a mean worm load of m are even less attractive. In the "together" situation, May showed the fraction paired ϕ_t to be:

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

The "separate" analogue cannot at present be expressed in closed form:

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

where $\theta_{ij} = 1$ if $i=j$

$= 2$ otherwise.

The corresponding equation for Macdonald's situation was given in Chapter Two as:

$$\phi_m(m) = 1 - e^{-m}[I_0(m) + I_1(m)]$$

with $I_j(x)$ the Modified Bessel function of order j.

While equations involving $\phi_s(m,k)$ and $\phi_t(m,k)$ will be needed later, attention is now focussed on $\Pi_t(j|m,k)$ and $\Pi_s(j|m,k)$.

By means of the multiplying factor of 0.763 discussed before, the worm pair count for each individual is obtained. For one given year, the log likelihood of the multinomial distribution of worms has been maximized with respect to parameters m and k. The clumping parameter k for both situations was estimated over all age groups for each year. A strong case could be made for obtaining separate estimates of k within each age group and pooling these if they are not dissimilar. It is felt that the data considered here involved too few infections within each age group for all the years to use this precise approach. While there is no theoretical evidence as to possible correlations between the parameter estimates m and k, numerical results (based on the second derivatives) showed little correlation. It is expected that this pooling approach produces representative values for k, despite different mean worm loads in age groups within years.

If P_i is the probability a host has i worm pairs and there are n_i of these hosts, the log likelihood is given by:

$$L = \log n! - \sum n_i! + \sum n_i \log P_i \qquad \text{and } n = \sum n_i$$

where the P_i are given by Π_t or Π_s from equations (IV-1) or (IV-2).

A note on the computation of these probabilities is warranted. In the separate case, the hypergeometric function satisfies the recursive formula:

$$F(k+j+1,1;j+2;\alpha') = \frac{(j+1)}{(j+k)\alpha'} \{ F(k+j,1;j+1;\alpha') - 1 \} \qquad \text{(IV-3)}$$

In numerical work, however, this was found to be unsatisfactory, leading to considerable rounding errors. (This was traced to the factor outside the brackets multiplying a rounding error from the subtraction within the brace

brackets by a factor greater than one.) Similarly, although there is no single recursive formula as (IV-3) to calculate $F(k+2j,1;j+1;\frac{\alpha}{2})$, an algorithm can be based on two of Gauss's relations for contiguous functions. (For example, see equations 15.2.10 and 15.2.20 of Abramowitz and Stegun.) When attempted, it was found that rounding errors accumulated too rapidly to permit their use as well.

As a result, minimization was accomplished using the series expansions for Gauss's hypergeometric function. The negative log likelihood was minimized with the CERN programme MINUITS on the University of London Computing Centre CDC6600 computer. Table IV-4 presents the estimates for the ten surveys for both "separate" and "together" situations along with their approximate standard errors. (These are obtained from a numerical approximation to the square root of $-\partial^2 L/\partial k^2$ or $-\partial^2 L/\partial m^2$.) Furthermore, Table A-2 presents the observed and fitted distributions of worm pairs. Comments on the fit are given in the fifth chapter.

5) Mean Worm Load

The process of estimating the worm load from a worm pair load is not straightforward. While a host with i male worms and j female worms is assumed to have $m = \min(i,j)$ worm pairs, given that a host has m worm pairs, there are several possibilities for the total number of worms i+j. For a host with worm pair burden m, one possibility might involve computing the conditional probability of $i+j \geq m$ given there are m pairs, and selecting the maximum value. This is not employed here, as such an elaborate procedure is not in keeping with the crude estimates employed elsewhere. Alternatively, once values are obtained for k in the two cases, the proportion paired $\phi_s(m,k_s)$ or $\phi_t(m,k_t)$ is calculable. The worm burden from each

host is approximated by inverse interpolation (and doubling) from the worm pair load and pairing probability relationship. The most glaring discrepency is possibly that people with no worm pairs are assumed to carry no worms at all. As before, reliance is placed on the approximation sufficing in pooling the values eventually for mean worm loads for age groups. Table IV-5 presents the mean worm pair loads and derived mean worm burdens for the "together", "separate" and "Poisson" situation.

6) Miricidial Release (λ_1)

The transmission of infection between definitive host and intermediate host has been arbitrarily split into the number of ova released daily by a given paired female, and the probability that one ovum results in an infection of a given snail. In the estimation of the former (λ_1), only the number of ova released into the faeces is considered, and considerations of viability of the eggs are deffered until estimation of latter (p_2).

The calculation of mean worm pair load from egg burden requires the assumption that each pair produces 250 eggs daily, and of this 65% reach the faeces. Thus, a value of 162.5 is gien to λ_1.

It is interesting to compare this value to those used by Macdonald and Hairston. On line six in the second paragraph of page 493, Macdonald (1965) clearly assumes that each paired female produces 1000 eggs. Unfortunately, it is impossible to recover the proportion of these escaping the body. Hairston's (1965) calculations are based on indirect results. Dairy production of eggs for S. mansoni was assumed to be 10% of that of S. japonicum, which had a value of 1400 eggs per day. (This is on page 55, right column, paragraph 4, lines 3 to 11, but note the first 140

on line 10 is a misprint for 1400.) Hairston also assumes that 30.3% of eggs escape from the body (page 57, left column, paragraph 1, lines 2 to 4 and page 56, right column, paragraph 1, lines 2 and 3), and thus the number of eggs daily released per paired female is 42.4.

7) Probability of Miricidial Success (p_2)

The calculation of this parameter requires a considerable number of assumptions of homogeneity in time and space. The present calculation is taken to apply similarly over all years, and identically for all eggs regardless of where they are released. Naturally, this is a prime area for future development of models.

For present circumstances, the proportion of successful miricidia is obtained from the number of snails newly infected each week and the weekly egg release. The latter calculation involves the use of some data twice in the model: a procedure that is used reluctantly. It seems particularly hazardous to employ structures in the model to derive estimates with an ultimate view to studying appropriateness of the model. This tautologial approach can only lead to over-confidence in a formulation as, when this is done frequently, the model can only "verify" itself (and thus situations of poor agreement are surprising). This type of approach was employed by Hairston (1962) and Huffman (1972). It is used here as the only available expedient.

By means of catalytic curves, Sturrock and Webbe (1971) report weekly snail incidence of 40,70,28,40 and 25 new infections per thousand snails for April and May 1970 (especially Table II, page 194). As reported above (Table IV-3), the standing crop of snails in 1970 is assumed to have been

76,000. Taking the value of 40 as representative of the five observations above (median = 40, mean = 40.6), each week there are 3040 new infections or successful miracidia for the entire region.

Table IV-6 demonstrates the calculation of the total number of viable miracida released per week. Upatham et al (1976, Table 2) published data reporting hatching rates for S. mansoni eggs on St Lucia. The snail incidence rates were based on studies near the 1970 survey, and thus the estimations of the host population were those taken at the survey, and not mid-survey.

Combining these results, one has a probability that a miricidium successfully infects a snail as $3040/1.614 \times 10^6 = 1.884 \times 10^{-3}$, p_2, the probability that a miracidium infects a given snail is $3040/(1.614 \times 10^6 \times 7.6 \times 10^4) = 2.478 \times 10^{-8}$. The success rate on a per snail basis is, of course, independent of the standing crop, i.e., $2.478 \times 10^{-8} = 40/(1000 \times 1.614 \times 10^6)$.

This per snail rate should not be compared to values used by Hairston and Macdonald. A preferred value is the probability of eventual success of a miricidium, 1.884×10^{-3}. Macdonald considered a value of 1.25×10^{-3} (Ek_1) but it is unclear whether or not allowance for hatching was made here, or in his daily egg release rate. The value employed by Hairston (1965) was 2.59×10^{-2}.

It is possible to combine estimates of λ_1 and p_2 with N_2 to compare values used in different models (thus overcoming the inability to declare which of Macdonald's parameters, Ek_1 or z_1, allowed for hatching.) The value of $N_2\lambda_1 p_2$ is the number of snails infected in one day by a paired

female schistosome. Hairston's value was (140 x .303 x 2.59 x 10^{-2}=) 1.10, Macdonald used (1.25 x 10^{-3} x 1000 =)1.25 and the current value is (162.5 x 1.884 x 10^{-3} =) .306 .

8) Death Rates of Snails (μ_2, μ_2', μ_2'')

The intermediate host for the transmission of schistosomiasis in St Lucia is Biomphalaria glabrata, and values for some of these parameters (μ_2, μ_2') have been derived by an extension of Meunch's catalytic models due to Cohen (1973). These were published by Sturrock, Cohen and Webbe (1974). For present purposes, the assumption is made that $\mu_2' = \mu_2''$. Weekly values ($7\mu_2$) varied between 0.0043 and 0.0938 with a median of 0.0071. Infected snails produced weekly values of 0.0220 to 0.1801, with a median of 0.0584. The median values, converted to daily rates by division, used are: $\mu_2 = 0.001$, $\mu_2' = \mu_2'' = 0.00834$. The formulation of the model described in equations III-1 to III-11 does not require μ_2, and interest centres on the use of the remaining two (μ_2' and μ_2'').

These values differ considerably from those used by Macdonald ($-\log_e(0.95)$ =) 0.0513 and Hairston (1965, page 48), who obtained values from 0.0327 to 0.077 and employed the mean value 0.0563. It is unclear which, if any, species of snail Macdonald had in mind for his value, while Hairston considered Biomphalaria alexandrina . (The agreement between Hairston's value and Macdonald's is striking). The difference is better shown with mean lifespans of snails. Macdonald's value yields 19.5 days and Hairston's 17.8. Both authors assumed $\mu_2 = \mu_2' = \mu_2''$. The estimates herein applied are 1000 for uninfected snails (about 3 years) and 120 days for those infected. The properties of a system

like this are strongly dependent on the death rates (μ_1, μ_2, μ_2' and μ_2'') and one expects these low values of μ_2, μ_2' and μ_2'' will considerably influence any conclusions. (It is noted in passing that these values vary considerably from values published earlier by Sturrock (1973, page 185).)

9) Latency Period (τ)

No carefully controlled experiments have been reported studying the length of the prepatent period in Biomphalaria glabrata on St Lucia. Jordan (personal communication) has suggested a value of 35 days, and members of the biological team of the Research and Control Department feel this is satisfactory. Macdonald used a value of 25 days and Hairston used 35 (page 49).

10) Cercarial Release (λ_2)

Sturrock in 1975 (page 186) reports a study of cercarial output in naturally infected snails performed between 1967 and 1969. A wide range of cercarial output was found: from 2 to 2159. The value for λ_2 used here is Sturrock's reported mean of these observations, 336. On page 47 of his 1965 paper, Hairston ascribes a value of 3500 to λ_2. From considerations in Chapter Two, it is not clear what value Macdonald ascribed to this individual parameter.

11) Success Rate of Cercariae (p_{1_i})

The method of calculating this parameter is similar to that in estimating p_2 : the number of cercariae released per day is obtained and the number of successes is used as well. The former involves simplified

calculations, but the latter uses data from other studies.

The daily number of cercariae available is determined readily. The standing crop of snails for the years 1967 to 1970 has been noted above. These are combined with the value of λ_2 above to show daily cercarial populations in Table IV-7.

During these years, infectivity of the waters was being studied with sentinel mice. The animals were exposed to the streams and marshes for only one hour, then left several weeks for any infection to develop, and subsequently slaughtered to study the number of successful cercariae. Infection rates were calculated for three sites X, Y and Z (the latter two were re-named YZ marsh and YZ river). In Table IV-7 are summarized the numbers of succesful cercariae (i.e. worms found) and the number of mice studied.

For the purposes of extrapolating these results to human data, the surface area exposed per mouse-hour is calculated. Mice were trapped with only a head above water with the trunk and tail exposed. Taking a right-angled cylinder as a model for the mouse trunk (dimensions: 4cm high by 2.7cm diameter) and a right-angled cone for the tail (9cm high by 0.4cm diameter at base), the surface area exposed is given by:

$$SA = 2\pi r_{cy} h_{cy} + \pi r^2_{cy} + \pi r_{co} \sqrt{r^2_{co} + h^2_{co}}$$

with r_{cy} , h_{cy} the radius and height for the cylinder respectively, and likewise r_{co}, h_{co} for the cone. The value of SA used is 45.3 square centimetres. Table IV-7 summarizes both the mouse infection rates per cm^2-hour exposure and, after allowance is made for the standing crop of cercariae, the probability that a cercaria successfully infects a square

centimeter of flesh exposed for one hour.

A Research and Control study in 1975 (Goddard, 1977) provides data on human exposure. The region studied was not that considered here (it was primarily Grande Ravine in Riche Fond valley). Observations were made at sites frequented by females washing, and adult males were rarely noted. Three major assumptions are made: firstly, that the Grande Ravine data is applicable in the Ravine Poisson region, secondly that the female results alone are appropriate for both sexes, and thirdly, that values for 1975 are representative for all other years. From this study durations of exposure to infected water on an individual basis (as opposed to a per contact basis) are derived which are combined with information on surface area to obtain the total exposure, by age group, over the study period of forty-nine days of twelve-hour observations. These data, with results corrected to cm^2-hour exposure are displayed in Table IV-8. Lastly, the success rates per cm^2-hour based on sentinel mouse studies are multiplied by these figures to give the expected number of successful cercarial infections in different age groups, which are shown in Table IV-9. For modelling between 1967 and 1969, the 1968 results in Table IV-9 are used, following which 1969 and 1970 results are employed when modelling the corresponding years. The overall results are used when modelling 1971 and later years. The parameter in the model is in a per person basis, and thus p_{1_i} is given by the appropriate element in Table IV-9 divided by N_{1_i}.

Hairston uses a different method to obtain the total number of successful cercariae, with incidence figures in human populations. The value obtained (not on a per person basis) is 6.98×10^{-7} which is not

very different from entries in Table IV-9. While the use of sentinel mice as a basis of estimating success rates seems more straightforward the adequacy of a mouse as a model for human exposure is felt by some to be poor. It is suspected that humans are more susceptible than mice, and that these values of p_{1i} possibly underestimate the true values.

For the basis of a better comparison, it is worth noting that the chance an infected snail leads to a successful cercaria in the same day is given as (3500 x 6.98 x 10^{-7} =) 0.002443 by Hairston. Macdonald's estimates are expressed per metre of riverbank, and when allowance is made for a length of 1000 metres, a value of Ek_2z_2/L = (0.015/1000 =) 0.000015. The model considered here employs values ranging between .0000066 to .00061. The disparity between these figures may be due to the large differences in predicted snail standing crops, and reinforces impressions that better formulations (with appropriate estimation procedures) are warranted.

12) Death Rate of Schistosomes (μ_1)

Estimation of the death rate of schistosomes is lacking for the most part. Suggested methods and values are studied by Holford (1972) and Warren et al (1974). There was a surprising similarity in values mentioned by Macdonald and Hairston. The former explicitly states (page 493, paragraph two, line 6) a mean life of three years, and almost certainly used $r = \mu_1 = 0.001$. Hairston uses values obtained by catalytic model (1965b) which range from 0.10 to 0.336 (page 52, 1965a) per year, and uses (page 57, 1965a) the value 0.336. This corresponds to μ_1 = (0.336/365 =) .000921. Even though some doubts

arise as to the use of catalytic models for human hosts in schistosomiasis, as there seem to be no preferred values and these two agree, the current model assumes $\mu_1 = 0.001$.

13) Immigration of Worms (ε_i)

In preparing the data of people and intensities of infection, special attention has been paid to noting which individuals were from outside the area and the intensities of infection these bore. The intensity of infection was recorded as eggs per gram of faeces. These have been calibrated to worm pair loads by multiplication with 0.763 (see the section on estimation of m_i). As with mean worm loads for the entire population, the worm load for each immigrating person is estimated from the worm pair load. When divided by the total period the parameters would serve (548 days for 1967, 365 for all others) and the number of individuals, N_{1_i}, the instantaneous daily immigration per person in mean worm load, is obtained. The three sets of values according to the "together", "separate" and "Poisson" situations are summarized in Table IV-10.

14) Loss of People through Emigration and Death (δ_i)

Values of δ_i are obtained from the movement of individuals displayed in Table A-1. When corrected to a daily basis, the figures obtained are shown in Table IV-11.

15) Change of Age Groups by Individuals (η_i)

As above the values of η_i are obtained from Table A-1, corrected to a

daily basis, and displayed in Table IV-11.

Throughout, very rough techniques have been employed to estimate parameter and variable values. No measures of the dispersion of the estimates are provided where possibly considerable variation exists. The assumption of homogeneity has been invoked frequently as a simplifying approach. While these techniques are subject to criticism their use reflects the current nature of this specific area: there is much yet to be done. In the next chapter some idea of the dependence of the model to specific parameter estimates is gained when the sensitivity of some variables to changes in some parameter values is investigated.

The values of parameters and variables for each year are summarized in Table A-3 in the appendix.

Map of community in Ravine Poisson area. FIGURE IV-1

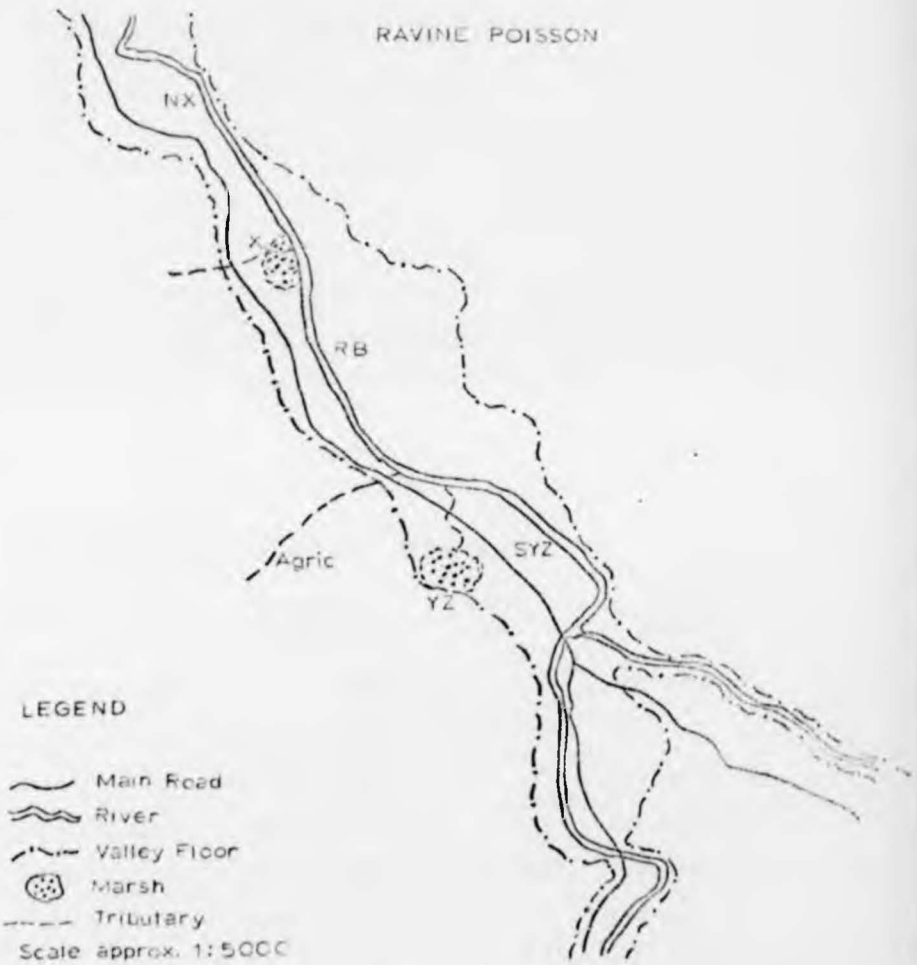
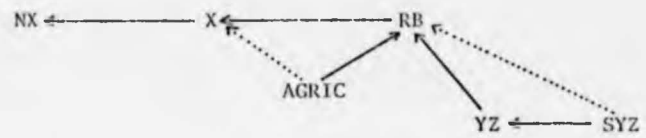


Figure IV-2

Flow of Infection Within Area Studied



——→ probable contribution of infection

·····→ possible contribution of infection

Table IV-1

Subareas within main Ravine Poisson Area

Sub area	Name	Household Numbers	Marsh Area	River Length
North of X	NX	1015 - 1026		500 meters
Marsh X	X	1027 - 1040	0.5 acres	
Riverbank	RB	1041 - 1063		300 meters
Agric stream	Agric	1064 - 1075		280 meters
Marsh-Stream YZ	YZ	1074 - 1099	1.25 acres	50 meters
River South of YZ	SYZ	1100 - 1125		150 meters

Table IV-2 Snail Survey Results

i) Average Standing Crops (No. of Samples taken)

	AREA		
	X	Y	Z
1967	140(14)	39(21)	33(15)
1968	15(2)	39(27)	12(21)
1969	31(24)	14(15)	3(23)
1970	188(3)	23(4)	3(13)

ii) Average Number of Snails Infected

	AREA		
	X	Y	Z
1967	1.71	.05	.13
1968	0	.07	0
1969	.33	0	0
1970	7.77	0	.08

iii) Infection Rates

	AREA		
	X	Y	Z
1967	.012	.001	.004
1968	0	.002	0
1969	.011	0	0
1970	.041	0	.026

Table IV-3 Standing Crops of Snails

	Number of Snails (N_2)	Number Patently Infected	Infected Proportion (y)
1967	90,000	450	.0050
1968	63,000	110	.0018
1969	29,000	73	.0025
1970	76,000	1700	.0222

Table IV-4 Fitted Parameters for Bradley-May's Distributions

Together	m̂	SE(m)	k	SE(k)	CORRELATION	L
1967	65.50	17.66	.1275	.02098	.00000	-655.65
1969	43.02	5.504	.5287	.06805	.00002	-898.07
1970	32.90	4.179	.5065	.06654	.00001	-883.64
1971	28.59	4.845	.2419	.03376	.00001	-865.19
1972	25.12	2.601	.5507	.06732	.00001	-1031.26
1973	21.51	3.433	.2474	.01571	.00001	-897.62
1974	21.20	.6447	.3884	.05195	.00000	-978.17
1975	14.86	3.419	.0902	.01402	.00103	-743.21
1976	2.873	.8861	.0516	.01228	.00018	-330.78
1977	1.027	.4509	.02756	.009993	.00181	-160.47

Separate	m̂	SE(m)	k	SE(k)	CORRELATION	L
1967	221.58	4.711	.2087	.02196	.00981	-679.08
1969	103.74	2.169	.5312	.009060	.18112	-897.69
1970	82.56	.7247	.5100	.004285	.03558	-886.60
1971	94.57	2.419	.2945	.004059	.00297	-879.20
1972	58.80	.9181	.5526	.04992	.00000	-1036.09
1973	68.86	.1660	.3013	.002757	.03500	-910.99
1974	56.89	.5302	.4235	.001788	.00079	-991.03
1975	56.63	.01755	.1666	.00001863	.00000	-780.79
1976	12.09	.05107	.1221	.0001359	.00000	-347.71
1977	4.735	1.174	.09071	.03985	.00000	-169.25

L = Maximized log likelihood

Table IV-5

Estimated Mean Worm Pairloads in Population

Age	1967	1969	1970	1971	1972	1973	1974	1975	1976	1977
0-4	1	4	1	0	0	0	0	0	0	0
5-9	13	4	3	9	3	3	0	0	1	0
10-14	151	90	37	21	13	7	11	9	1	0
15-19	45	32	46	44	42	32	26	12	2	1
20-29	14	12	17	15	16	17	19	13	5	2
30-39	31	17	14	9	6	6	10	8	0	0
40-49	3	4	4	4	7	9	3	2	1	0
50-59	2	4	4	5	6	9	9	13	0	0
60+	0	0	0	0	2	11	7	7	1	0

Estimated Mean Worm Loads - Together Situation

Age	1967	1969	1970	1971	1972	1973	1974	1975	1976	1977
0-4	2.0	8.8	3.6	.6	1.0	.4	.0	.6	0	0
5-9	28.0	10.6	7.2	19.6	8.4	7.0	1.2	.2	1.4	0
10-14	311.4	192.2	82.4	45.4	30.6	17.0	24.6	19.6	2.4	.2
15-19	94.2	71.6	101.0	94.4	92.8	68.4	58.6	26.4	3.4	2.6
20-29	30.8	28.8	40.2	32.8	37.6	36.8	43.6	27.2	10.2	3.6
30-39	65.0	39.6	33.0	21.0	15.4	14.0	24.0	16.8	.4	0
40-49	7.8	10.8	10.8	10.2	17.8	19.6	7.6	4.8	1.4	.8
50-59	5.6	10.8	10.8	12.0	14.6	20.2	22.4	27.4	0	.6
60+	0	0	0	0	6.2	24.0	17.4	14.6	2.4	0

Table IV-5 (Cont'd.)

Estimated Mean Worm Loads - Separate Situation

Age	1967	1969	1970	1971	1972	1973	1974	1975	1976	1977
0-4	8.4	20.2	8.0	2.0	2.2	1.6	0	3.4	0	0
5-9	124.4	23.4	15.8	68.8	18.2	23.2	3.0	1.2	9.0	0
10-14	1448.0	487.4	204.0	155.6	70.8	55.6	66.6	105.4	16.2	1.0
15-19	432.6	173.6	250.6	333.0	219.4	236.4	157.8	140.2	22.8	11.5
20-29	137.0	66.8	96.0	111.8	85.2	123.4	114.8	142.8	68.4	16.0
30-39	296.4	94.0	78.0	69.8	33.0	46.2	62.0	89.4	2.4	0
40-49	32.8	23.4	23.4	32.8	38.2	65.6	17.6	25.2	9.4	3.4
50-59	23.8	23.4	23.4	38.2	31.0	66.0	58.0	147.2	0	2.4
60+	0	0	0	0	12.0	80.2	43.8	76.2	16.6	0

Estimated Mean Worm Loads - Poisson Situation

Age	1967	1969	1970	1971	1972	1973	1974	1975	1976	1977
0-4	2.2	9.2	4.0	.6	1.0	.6	0	.8	0	0
5-9	30.2	11.4	7.6	20.4	9.0	7.6	1.2	.2	1.6	0
10-14	319.2	195.4	84.6	47.8	31.6	18.4	25.6	21.0	2.8	.2
15-19	97.6	73.6	103.4	97.8	95.0	71.0	61.0	28.6	4.2	3.6
20-29	33.0	30.2	41.8	34.8	39.0	39.0	45.6	29.8	11.6	4.0
30-39	67.8	41.2	34.6	22.6	16.6	15.2	25.6	18.4	.4	0
40-49	8.8	11.8	11.8	11.4	18.8	20.8	8.4	5.2	1.8	1.0
50-59	6.4	11.8	11.8	13.4	15.6	21.6	23.8	29.4	0	.6
60+	0.0	0	0	0	6.8	25.6	18.8	16.2	3.0	0

Table IV-6

Weekly Viable Miricidial Release - 1970

Age Group	Egg/Gram	Grams faeces per week	Number of Hosts	Proportion Hatching	Weekly Viable Miricidia Production
0-4	1.64	868	47	.422	28000
5-9	3.10	868	52	.422	59000
10-14	49.05	868	39	.422	701000
15-19	59.00	868	25	.422	540000
20-29	22.12	868	26	.325	162000
30-39	18.00	868	16	.325	81000
40-49	5.00	868	28	.254	31000
50-59	4.00	868	13	.254	11000
60+	0	868	4	.254	0
				Total	1,614,000

Table IV-7

Determination of Mouse Infection Rate

Daily Cercarial Populations

Year	Infected Snails	Cercariae Released/Snail	Total Cercariae
1967	448	336	151,000
1968	112	336	38,000
1969	73	336	25,000
1970	1694	336	569,000
Average	582	336	195,000

Infections in Sentinel Mice (no. of worms/no. of mice)

Year	X	YZ Marsh	YZ River	Overall
1967	74/350	8/329	0/325	82/1004
1968	1/463	0/482	4/476	5/1421
1969	23/497	2/478	3/478	28/1453
1970	49/282	0/302	0/232	49/816
Overall				169/4694

Year	Mouse Infection Rates	Pr(cercarial success per cm^2-hr exposure)
1967	1.80×10^{-3}	1.20×10^{-8}
1968	7.77×10^{-5}	2.06×10^{-9}
1969	4.25×10^{-4}	1.73×10^{-8}
1970	1.33×10^{-3}	2.33×10^{-9}
Overall	7.71×10^{-4}	3.94×10^{-9}

Table IV-8

Human Exposure Rates

Age group	m^2 per 49 half days	cm^2 per hour
0-4	.0463	.79
5-9	.0844	1.44
10-14	.2201	3.74
15-19	.3245	5.52
20-29	.2546	4.33
30-39	.5092	8.66
40-49	.2295	3.90
50-59	.1967	3.35
60+	.1086	1.85

Table IV-9

Probabilities of Successful Penetration by Cercaria (all x 10^{-8})

Age Group	1967	1968	1969	1970	Overall
0-4	.94	.16	1.40	.18	.31
5-9	1.70	.30	2.50	.33	.57
10-14	4.50	.77	6.50	.87	1.50
15-19	6.60	1.10	9.60	1.30	2.20
20-29	5.20	.89	7.50	1.00	1.70
30-39	10.00	1.80	15.00	2.00	3.40
40-49	4.70	.81	6.80	.91	1.50
50-59	4.00	.69	5.80	.78	1.30
60+	2.20	.38	3.20	.43	.73

Table IV-10

Daily Immigration of Worm Pairs per Person - All Values $x10^{-4}$

Age	1967	1969	1970	1971	1972	1973	1974	1975	1976
0-4	4.7	0	0	4.8	0	0	0	0	0
5-9	5.6	1.6	0	1.2	12.1	0	3.0	8.2	0
10-14	55.1	0	73.3	143.0	12.8	0	0	6.5	0
15-19	22.0	0	126.0	0	394.0	44.6	9.6	0	0
20-29	0	44.8	116.0	34.6	196.0	25.7	122.0	45.7	40.2
30-39	37.6	0	57.9	8.9	0	29.6	15.7	0	0
40-49	2.6	0	7.3	0	34.3	2.9	51.9	3.7	0
50-59	0	0	0	0	52.3	8.4	103.0	0	0
60+	0	0	0	0	222.0	0	50.6	0	0

Daily Immigration of Worms per Person - Together Situation - All Values $x10^{-4}$ (ε_i/N_{1i})

Age	1967	1969	1970	1971	1972	1973	1974	1975	1976
0-4	13.6	0	0	12.0	0	0	0	0	0
5-9	14.8	4.4	0	3.4	28.0	0	6.6	17.4	0
10-14	118.0	0	159.4	304.0	29.6	0	0	14.0	0
15-19	49.2	0	268.0	0	822.0	99.8	21.0	0	0
20-29	0	103.8	256.0	81.2	418.0	58.8	260.0	96.4	83.8
30-39	87.6	0	126.2	22.8	0	71.4	35.8	0	0
40-49	7.0	0	17.6	0	78.6	8.0	111.0	8.6	0
50-59	0	0	0	0	116.4	20.6	218.0	0	0
60+	0	0	0	0	484.0	0	115.8	0	0

Table IV-10 (Cont'd.)

Daily Immigration of Worms per Person - Separate Situation - All Values $x10^{-4}$ (ε_i/N_{1_i})

Age	1967	1969	1970	1971	1972	1973	1974	1975	1976
0-4	28.0	0	0	25.8	0	0	0	0	0
5-9	32.2	9.2	0	7.0	91.0	0	34.0	118.8	0
10-14	298.0	0	554.0	748.0	95.8	0	0	94.2	0
15-19	119.6	0	954.0	0	294.0	270.0	109.2	0	0
20-29	0	248.0	878.0	184.4	1456.0	155.2	1382.0	662.0	748.0
30-39	208.0	0	438.0	48.8	0	183.6	180.4	0	0
40-49	15.2	0	56.6	0	258.0	18.8	590.0	55.0	0
50-59	0	0	0	0	390.0	52.6	1162.0	0	0
60+	0	0	0	0	1648.0	0	582.0	0	0

Daily Immigration of Worms per Person - Poisson Situation - All Values $x10^{-4}$ (ε_i/N_{I_i})

Age	1967	1969	1970	1971	1972	1973	1974	1975	1976
0-4	14.6	0	0	12.6	0	0	0	0	0
5-9	15.8	4.8	0	3.8	30.2	0	7.8	19.2	0
10-14	120.0	0	166.4	308.0	32.0	0	0	15.8	0
15-19	50.6	0	276.0	0	838.0	103.4	23.4	0	0
20-29	0	108.2	268.0	84.4	432.0	61.8	282.0	106.0	93.4
30-39	91.2	0	122.2	24.6	0	76.2	42.0	0	0
40-49	7.6	0	19.4	0	84.6	9.0	119.8	11.0	0
50-59	0	0	0	0	123.4	22.4	234.0	0	0
60+	0	0	0	0	508.0	0	134.8	0	0

Table IV-11

Daily Loss of Human Hosts through Death and Emigration ($\delta_i/N1_i$)

All Values $x10^{-5}$

	1967	1969	1970	1971	1972	1973	1974	1975	1976
0-4	16	0	0	0	14	29	12	22	15
5-9	7.4	10	9.9	0	26	12	22	25	32
10-14	0	0	6.0	0	27	15	14	16	34
15-19	0	32	0	0	58	16	12	32	70
20-29	12	0	9.1	7.2	59	47	49	70	63
30-39	11	0	0	0	15	0	0	8.2	29
40-49	6.5	0	0	0	9.8	9.6	38	9.3	41
50-59	0	0	0	0	0	21	20	9.3	26
60+	0	0	0	0	23	18	28	25	12

Daily Loss of Human Hosts through Changing Agegroups ($n_i/N1_i$)

All Values $x10^{-5}$

	1967	1969	1970	1971	1972	1973	1974	1975	1976
0-4	55	71	39	12	75	58	49	82	20
5-9	22	83	30	28	60	40	48	60	64
10-14	26	56	32	58	21	55	57	41	30
15-19	41	54	49	59	33	39	30	54	29
20-29	0	0	27	7.2	6.5	20	36	32	10
30-39	22	0	31	44	30	59	11	16	0
40-49	0	9.6	0	64	59	29	19	19	52
50-59	0	21	22	38	13	21	30	9.3	27
60+	-	-	-	-	-	-	-	-	-

Daily Gain of Human Hosts through Changing Age Groups ($\xi_i/N1_i$)

All Values $x10^{-5}$

	1967	1969	1970	1971	1972	1973	1974	1975	1976
0-4	-	-	-	-	-	-	-	-	-
5-9	52	62	35	81	42	32	30	53	16
10-14	38	130	38	41	85	50	61	69	60
15-19	28	75	49	84	33	86	72	54	47
20-29	71	62	46	50	26	34	30	54	26
30-39	0	0	47	15	15	44	67	49	15
40-49	13	0	18	27	20	38	9.6	19	0
50-59	0	21	0	130	76	32	20	19	44
60+	0	78	50	68	23	35	42	12	35

Chapter Five:- Model Results

In Chapter Four, the values for parameters and variables to be used in the model were derived. In the first part of Chapter Five, the appropriateness of these values is considered. The adequacy of the model described is then studied in two ways: firstly, for each year studied after 1967, it is possible to compare observed infection rates (mostly in humans) with predicted values. Secondly, the equilibrium situations can be studied to explore how realistic these may be. In addition, it is possible to show the effects that changes in the parameters might have on the proportion of snails patently infected at equilibrium.

1) Parameter and Variable Values

a) Related to Snails

Consideration of the observed numbers of snails will cause one to doubt the validity of assuming that N_2 is constant. The infected proportion of snails is very small, and varies considerably from year to year. The largest values of 2.2% occurs in the 1970 data, where the number infected (1700) is nearly four times as large as the next highest (450), which is itself four times higher than the next (110). That this variation is considerable is also emphasized when one studies the intensity of human infection in the associated years. It is clear that the intensity in 1970 was not four times that of 1967, although the ratio of infection rates in snails is 4.4. As there is considerable extrapolation to obtain population values, and as there is evidence of considerable variation, this particular facet of the model is subject to question. No estimates of sampling error were attached to these values, but once extrapolated, the

distribution of the population estimate would be particularly disperse.

The death rates of uninfected and infected snails were chosen to be 0.001 and 0.00834 respectively. These correspond to mean life spans (assuming, as this model does, survival is exponential) of 1000 and 120 days respectively. A mean life span of about 3 years for uninfected snails (which were much more common) also suggests there is considerable sampling error in estimates of N_2.

b) Related to Humans

The human census for the area is subject to fewer errors than the snail census. As well, any errors are not magnified by the process of extrapolation. The overall number of people determined by surveys increases monotonically from 218 in 1967 to a maximum of 414 in 1976 with 413 observed in 1977. This may either be due to improved survey collections or a genuine increase in population in the area.

Much more hazardous, however, is the task of estimating the mean worm load for each year. This involves several steps, each introducing error and possible violations of assumptions.

In obtaining mean egg burdens for each age group and each year, there is considerable estimation of missing values. Although aesthetically one would seek to base observations purely on data that is known, in this case there would be few well known values. Indeed, there is an inconsistency in the method of obtaining the values used, in that this procedure was itself a "modelling" process. It has been noted that some assumptions (for example that a missing value between two years with the same observation is identical to the other two) are contrary to those made

in the main model. As always, expediency is used to explain this choice, and it is hoped that this effect will "average out" when all cases are considered.

The process of obtaining the number of worm pairs from egg counts is naturally a dubious one regardless of the method employed. For present purposes, one method has been used which has been employed elsewhere (Macdonald, 1965a). The mean worm pair loads for the most part do not appear to be grossly unrepresentative, even when compared with Cheever's (1968) studies. One may readily question some of the particularly large values, particularly in the teenagers for 1967 and 1969. These tend to call into question the validity of the linear assumption between worm pairs and egg loads. Naturally, one expects to be able to improve this aspect of this model (as with all others) when this point is better understood. Given this assumption, while some intermediate parameters may be questionable, the overall results are not counterintuitive. The observed distributions of worm pairs are shown in Table A-2. It is immediately seen that the data do not follow simple distributions. Some examples of suspect observations are the null result in 1969 for 20-29 pairs, or the count of 58 for 40-49 pairs in 1970. It is believed that this arises from the restricted set of possible egg load results being multiples of ten, and the procedures to estimate missing observations.

The step from worm pairs to worms invokes the pairing distribution assumptions. The outstanding assumption made here is that values of k (regardless of the situation, "together" or "separate") obtained from an entire year's sample are representative of the age groups' values. There is an unfortunate arbitrariness about this parameter in that it affects

transmission but, as yet, has not been linked to any facet of the transmission. If the effect of clumping on the transmission in the area studied is large, there may be cause to reconsider this point. If not, and in light of its arbitrariness, it is hoped that this step is not subject to much concern.

Bradley and May (1978) suggest conditions in which the "separate" and "together" pairing situation occur. When transmission is low, there may be few patently infected snails. As all cercariae from one snail are of the same sex, in the community there will be few foci of water infected by cercariae of one sex, possibly leading to the "separate" pairing situation. At higher levels of transmission, all water will be infected by both male and female cercariae, a situation favouring the "together" pairing situation. In Table IV-4 are found the maximized log likelihoods of worm distributions in hosts. One might expect a transition of higher likelihood from "together" to "separate" from 1967 to 1977 as transmission was reduced by molluscicide. In all cases except 1969 the "together" situation yields a higher likelihood, however there are not large differences in any particular year. It may be that by 1977 transmission was not sufficiently lowered to levels where "separate" pairing may occur and the numerous assumptions and coarseness of egg count results (multiples of ten) make differentiation between situations difficult.

The estimates of immigration and emigration of human hosts are hopefully representative. The importance of this consideration is underlined by studying the 60+ age group, where a rise in mean worm pair loads occurs in 1973 after a rise in the arrival of infected hosts from elsewhere.

c) Transmission from Humans to Snails

The estimation of transmission parameters from man to snail and vice versa is a study still in its infancy, but readily capable of much study. (This is, for example, contrary to the study of the relation between worm pair loads and egg release. While still relatively unexplored, this topic is not easily investigated.) In this study, the traditional approach, based on a somewhat tautological argument, has been employed, as was done by Hairston (1962, 1965). Not only does the estimation suffer from this technique, but also estimates of daily miracidial concentrations and penetration rates in snails are probably subject to large variation. In using an extrapolated estimate of miracidia released and an extrapolated number of snails infected, one necessarily has a suspect figure. While the similarity of the current value to Macdonald's and Hairston's figure is striking, this really does not lend much additional validity to the value. It is assumed that the chances that one worm pair infects a given snail are constant for the entire complex, and thus any difference in values may reflect the size of the area considered. (One is more suspicious at the agreement of the figures than reassured.)

d) Transmission from Snails to Humans

The two prime areas of concern are the use of the mouse model and use of special exposure data. (This tacitly assumes that the cercarial release rate is much less subject to error.) As mentioned above, the homogeneity assumption for the entire complex is a simplification of the model that is unappealing. It is interesting to note that Macdonald used

a different explanation that amounted to a similar assumption.

There is a strong suspicion amongst the staff at Research and Control that the mouse is less prone to infection than the human. Indeed, infection results were so low that sentinel snail studies were discontinued in the area around 1970. This suspected under-estimation is of possibly considerable importance when extrapolated to surface area to humans.

The exposure rates for humans are used for all years and are drawn from a study in another area. Furthermore, the data pertained only to females and it was assumed that males would be similarly exposed. This may not be the case: data presented here reflect mostly exposure for the sake of washing clothes. There is a preponderance of females aged 30-39 exposed as a result of this, and this may not be so for males. The assumption is one of necessity however. The areas where observations were noted were predominantly residential and a project to follow male (occupational) exposure would possibly be poor return for the resources required. Secondly it is not thought appropriate to use "correction factors" for data relating male and female exposures elsewhere as any relationship is probably strongly determined by local customs and environment.

The shape of the curve of exposure by age group ($p1_i$) does not resemble that of the empirical age by intensity of infection curves, in that the largest exposures occur in older individuals (30-39 years). There are instances where there is greater similarity between such curves (see for example Jordan, 1972). One of the uses of a modelling

approach is to study the dependence of mean worm loads on exposure when allowance is made for other factors (such as the immigration or emigration of worms). When allowance is made for these factors it may be the case that unpromising age exposure curves result in familiar age-intensity of infection curves.

2) Predicted and Observed Values

It is possible to take one survey's results as an initial situation and follow the transmission of infection until the next survey, and then compare observed and predicted results. This has been done for each set of data using inter-survey periods of 365 days for all except the first where 548 (= 1.5 x 365) days are assumed. The aim is to study the model's accuracy not only under natural circumstances (the first two cases, 1967-1969 and 1969-1970) but also under a control scheme (1970 onwards). Thus, one is able to see if the model responds realistically when the system is "pushed" (Bradley, 1972) as well. The results under the various pairing situations appear in Table V-1.

There tends to be an overestimation of intensity in humans for all three pairing situations in the 1967 to 1969 data set. In all three cases, predicted values for hosts over 15 years of age exceed observed values. (It is interesting to note an over-estimate in the 10-14 year-old class (m_3) for the "separate" situation and under-estimates for the "together" and Poisson cases.) It is not easy to isolate any particular aspect of the model which may lead to this. When the overall shape of the predicted age by intensity curve is compared to both the human exposure rates (p_{1_i}) and observed age by intensity curve, it appears more like the former. Possibly the estimates of p_{1_i} are

poor and better data would provide a better fit. Alternatively, a model allowing for variable exposure still over-estimates in the older age groups which may be evidence that an immune response occurs in these hosts. These comments are qualitative and can be based on comparisons of exposure by age and intensity by age curves. It is somewhat satisfying to note that the model does not uniformly over-estimate, and produces values that are not unreasonable. The values predicted for the 60 years and older age group are much too large regardless of the pairing situation. This is thought to be due to the few cases (3) on which the mean is based and the relatively large value of p_{19} used, which is over twice that of p_{18}.

In order to investigate the dependence of the predictions on immigration and emigration of worms, predictions have been made keeping ε_i and δ_i at 0 for all age groups. Minor deviations from the unrestricted predictions are noted, and it appears to be the case that the infection rates predicted arise mostly from internal sources.

The most glaring discrepancy must be that found between observed and predicted proportions of snails patently infected. This is frequently found in models of this type: that snail infection rates need to be much higher to support internal transmission than those values found in nature. Barbour (1978) has considered models specifically attempting to study this problem. An area under consideration was split into subareas (ponds) each with separate areas of accessible water. The proportion of infected snails is minimized when heterogeneity is ignored and Barbour outlined an example where the proportion of infected snails was multiplied by a factor between two and three when allowance was made

for heterogeneity. It is for this reason that interest is focussed on critical points determined by values of y and not worm loads.

Observations of the 1969-1970 predictions differ considerably. There is now a uniform underestimation in the older age groups, possibly arguing counter to an allowance for immune effect. The agreement between observed and predicted is much better than the previous instance, and the mean load for people 60 years and older is much lower. One striking anomaly is noted in the 15 to 19 year age group, where a decrease in worm loads was predicted, but an increase occurred. This is not due to immigration from outside, but to the transition of particularly heavily infected individuals from the previous age group. (It is assumed that transitions are uniform across the range of worm loads in the preceding age group. In this case, loss of the heavily infected individuals produced an under-estimate in the 15 to 19-year olds, and an over-estimate in the 10-14-year olds.) As before, the predicted proportion of infected, patent snails is much larger than that observed.

Despite the numerous parameters that are estimated, and the many steps modelled, the predictions of human infection are not unreasonable when the natural course of the disease is under study. The over-estimation or under-estimation of several neighbouring age groups (especially the older) indicates that there is a systematic error. There appears to be little to choose, given this evidence, between the various pairing situations. In both cases, the effect of ignoring immigrating and emigrating worms had minor effects on the predictions, and it is concluded that the predictions were more reliant on the parameters of transmission internal to the area.

Shortly after the survey in 1970, the Research and Control Department began a molluscicide campaign that effectively eliminated all snails in the valley. This was modelled by letting N_1 equal zero, and predictions were made for the 1971 survey results.

There does not appear to be any consistent over or under-estimating for the older age groups. With the elimination of snails, one is modelling the decline in infection as schistosomes die out, altered by possible immigrations, emigrations and changes in age groups by hosts. (Thus, one is relying heavily on the parameter μ_1.) While the deviations do not appear to be overly large, there is evidence of anomalous behaviour. All mean loads are observed to decrease except for the 5 to 9-year olds and the 50 to 59-year olds. Decreases, however, are predicted for these classes, and all others except the 20-29-year olds. This applies for 'together' and 'Poisson cases but not the separate' case.

The next year (1971-1972), provides another test of the snail control effects. For the "together" and "Poisson" pairing situation, there appears to be an underestimation for older age groups. For those 40 years and older, there is an increase observed in mean worm loads over those at the start. Those aged 40 to 59 have losses predicted under all pairing assumptions, and those 60 and older have predicted gains too small in magnitude. This will possibly cast in doubt the treatment of immigrating worms.

In subsequent years, immigration and emigration of infection tends to affect the observed values. This is particularly noticeable in the oldest age group. Predictions by the model tend not to be wholly unreasonable, but one cannot feel that better fits would be more

satisfying. In one year, there appears to be a preponderance of over-estimation, (1975-1976) and in another, under-estimation (1972-1973). The "separate" pairing situation leads to uniform under-estimation in 1972 to 1973 and considerably more under-estimation in 1974 to 1975. The differences between "Poisson" and "together" situations are less distinct. At the lower levels of infection, differences between predictions including and excluding immigration and emigration effects become more marked, indicating the importance of these factors at these low levels.

3) Asymptotic Results

For the nine sets of data, it is possible to investigate the existence of equilibrium populations and the expected mean worm loads for these. Table V-2 summarizes these values for the various pairing situations and Figures V-1 to V-9 display the graphical analysis.

The first two sets of results, 1967 to 1969 and 1969 to 1970 are quite different from those later. In all diagrams, there is only one intersection, and the breakpoint phenomenon does not occur. For years 1970 to 1971 and later, it is apparent that any infection is solely due to immigration of worms. When this occurs, the curve for Wa, irrespective of the pairing situation, is independent of y. Years prior to these, before mollusciciding was performed, have Wa curves that do depend on y. While one is not surprised to find the "together" and "Poisson" curves behaving similarly, as values of k for both "separate" and "together" situations were estimated for each year separately, no fixed relationship can be expected in all nine results. A particularly

startling disparity is noted in the 1967 to 1969 results. In Table A-2, the predicted distributions of worm pairs do not appear greatly dissimilar, and thus the estimate of "k" seems reasonable in both cases. The discrepancy is possibly ascribed to the differing behaviour of the pairing probabilities at large mean worm loads, which is most applicable to 1967-1969 results.

As for the predicted results, so too here, the equilibrium proportion of patent snails is much too high to be intuitively appealing. (Indeed, for years when N_2 is assumed to be zero, the use of y is a measure of infectivity is entirely abstract and one may prefer to consider values of W.)

For the years of snail control, the eqilibrium values of m_i follow the patterns of immigration and emigration of worms. These provide no test of the model to produce the characteristic unimodal age by intensity of infection curve. For 1967 to 1969, the distribution of infection intensity does not have a peak in the teenage years. The results follow the distribution of p_{1_i} and immigration-emigration effects are minimal. (The equilibrium value of m_9 is particularly large. As immigration and emigration do not occur, and as there are no transitions from the eighth group, the the value is a solution of

$$\lambda_2 N_2 p_{19} y^* - u_1 m_9 = 0$$

or $.001m_9 = .055002$. This high value is attributable to a large number of snails (N_2) and large values of $p_{19}(.6288 \times 10^{-8})$.) The main conclusion is that the distribution of equilibrium mean worm loads across age groups strongly depends upon the distribution of exposure across these groups. If exposure distributions like those considered here fail to

produce the same shaped curve as age intensity of infection frequently do, then exposure is not alone sufficient to be added to the Macdonald-Nåsell-Hirsch formulation to explain transmission.

4) Sensitivity of Model to Parameter Values

As has been mentioned in the second chapter, Macdonald concluded that transmission of infection was sensitive to changes in snail count, exposure and schistosome lifespan. The Nåsell-Hirsch formulation of this model involved the separation of parameters into two transmission factors T_1 and T_2. The sensitivity of transmission (in terms of change of asymptotic mean worm load of hosts) to changes in various parameters could be restricted to the study of sensitivity to T_1 and T_2. Whereas the former studied sensitivity of a selected parameterization by numerical integrations (see particularly his Figure 5), and the latter studied sensitivity independent of any specific parameterization, it is convenient here to explore the behaviour of the asymptotic proportion of snails patently infected (y^*) as certain parameters are changed in the 1967-1969 situation.

Macdonald considered the use of a joint chemotherapy and mulluscicide campaign. He chose to study this by reducing the number of snails (N_2 here or SL in his notation) and decreasing the schistosome lifespan (by increasing μ_1 here or r in his notation). The changes in y^* as N_2 is changed for various values of μ_1 are summarized in Figure V-10 to V12 for the "together", "separate" and "Poisson" pairing situations respectively.

It is noted that under no circumstances is the breakpoint behaviour

displayed. As well, the values of y* seem particularly large. With a schistosome lifespan of 1000 days, as the population of snails (N_2) nears eradication, the value of y* is between nine and ten percent in the "together" situation. Changes in y* as N_2 is altered are must greater in the "together" and "Poisson" pairing situation, particularly with longer mean life spans of worms. The "separate" pairing situation is much less responsive. In all cases, a reduction of schistosome lifespan to 250 days produces much lower values of y* and marked insensitivity to N_2 in the "separate" and "Poisson" pairing situation.

If it assumed that there is no immigration or emigration in the above system, though allowance for age group tr a nsition is still made, dramatically different results are obtained. Figures V-13 to V-15 summarize these results. Solid lines represent upper (stable) equilibrium values of y* and dashed lines represent (unstable) breakpoint values of y*. A solid line corresponding to y* = 0 for all N_2 is omitted in these logarithmic plots, which would represent the other stable equilibrium situation.

As before, the "together" and "Poisson" pairing situations appear alike while "separate" results are obviously different. In the "separate" case, no transmission is possible with snail counts even doubled except when the schistosome lifespan is 2000 days.

For "together" and "Poisson" cases, transmission is possible with schistosome lifespan halved (albeit only with large snail populations). The curves for the "together" case are uniformly to the left of those for the "Poisson" case. Values of y* at breakpoint washout are lower as well. Both observations are in keeping with the clumped "together"

model, being more stable than the "Poisson" model. The value of y* appears to change with changes in the values of N_2 regardless of the value of μ_1. The value of y* where breakpoint washout occurs appears to be relatively insensitive to changes in value of μ_1.

By splitting up the definitive host into age groups, one is unable to summarize transmission factors by T_1 and T_2 as did Nåsell and Hirsch. (The values of p_{1_i} affect T_1 and those of N_{1_i} affect T_2.) Nevertheless, some parameters are always considered together and the sensitivity of y* to both requires only one be studied.

One fortunate instance of this is the linking of the p_{1_i} with N_2 (and λ_2). Recent studies in St Lucia (Jordan, 1975) have involved the effect of provision of water supplies on the dynamics of transmission. It has been noted above that the resultant age-intensity of infection curve depends strongly on the values of p_{1_i}. If one considers the effect of water supply provision to be a proportional reduction of exposure for all age groups (that is p_{1_i} is reduced by the same fraction regardless of i) then one can study the effects on y* from the results obtained by changing N_2. Figures V-10 to V-15 and relevant remarks can be applied to changes in p_{1_i} as well as N_2.

It is interesting to examine the methods modellers have used to relate changes in parameters to field "control" situations. As remarked above, Macdonald chose to model the effect of a chemotherapy campaign through changes in his r or the current μ_1, and molluscicide through changes in his SL or the current N_2. A similar line is taken by Nåsell and Hirsch (1973 esp. page 447). It is possible to consider different

changes in the model in an attempt to mimic the same field situation.

Consider firstly the effect of chemotherapy. One of Macdonald's recommendations was to reduce mean worm loads to below the breakpoint and eradication would occur. Alternatively, it was noted that if the mean lifespan of schistosome was sufficiently reduced, the breakpoint would "wash out". As the effect of the first case (lowering m) is to leave a situation wherein sufficient increase in mean worm load (through immigration) would cause a re-establishment of infection, while the second case (increasing μ_1) would not, this appears to be a relevant question. One might consider adjusting μ_1 only when it is known that should transmission be lowered (even eradicated) surveillance and chemotherapy would continue. Otherwise, chemotherapy may best be thought of as a means of lowering mean worm load below a breakpoint (if it exists) and not affecting the parameter μ_1 , which is assumed to take biological values unalterable by intervention.

If one does study the effect of chemotherapy by altering μ_1, then it does not seem unreasonable to study the effect of molluscicide by altering μ_2, μ_2' and μ_2'', rather than by changing N_2 . May (1977) has pointed out that such systems as this considered here have a "responsiveness" determined strongly by parameters μ_1, μ_2, μ_2' and μ_2''. In the Nåsell-Hirsch study (1973) changes in N_2 affect transmission factor T_1 while changes in μ_2 affect T_2 and thus this is an important question. (If both N_2 and μ_2 affected the same transmission factor, it would not matter which was assumed to change under molluscicide programs.) In Macdonald's (1961) discussion of a malaria model, this distinction is made (especially on page 758) while no mention is made with reference to the

schistosomiasis model in the same paper or in 1965.

As it has been assumed that $\mu_2' = \mu_2''$, it is possible to study the responsiveness of y^* to simultaneous changes in both μ_2' and μ_2'' for various values of μ_1 . The results are displayed in Figures V-16 to V-18 and corresponding to the case where there is no immigration and emigration, in Figures V-19 to V-21.

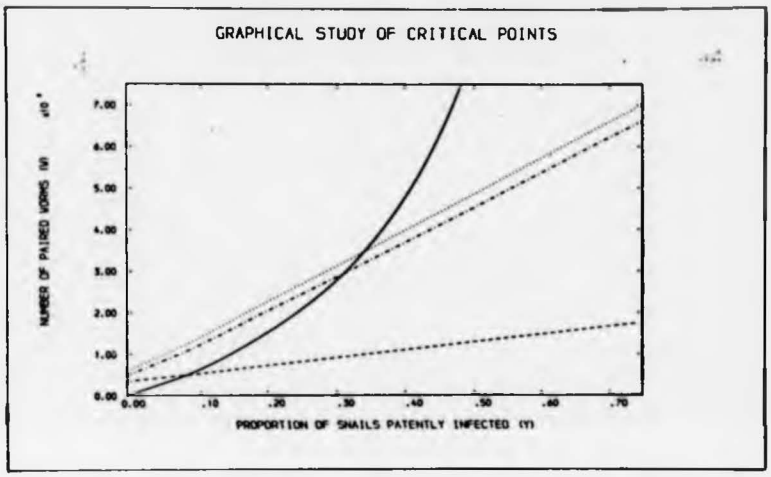
Comparison of Figures V-16 to V-18 with V-10 to V-12 respectively reveals that y^* is much more susceptible to changes in μ_2' and μ_2'' than N_2 regardless of which pairing situation is assumed. In this example, the difference between using μ_2' and μ_2'' or N_2 would affect decisions on control strategy. In Figure V-10, the asymptotic level of infected, patent snails y^*, is greater when N_2 is halved than when $1/\mu_1$ is halved. On this basis chemotherapy (changing μ_1) seems more productive than molluscicide (changing N_2). In Figure V-16, y^* is greater when $1/\mu_1$ is halved then when snail lifespan is halved (μ_2'' and μ_2' are doubled). Here molluscicide seems preferable to chemotherapy. While these findings pertain to the "together" pairing situation, like observations can be made in the "separate" (comparing Figures V-11 to V-17) and "Poisson" situation (comparing Figures V-12 to V-18).

Figures V-19 to V-21 parallel Figures V-13 to V-15. Breakpoint behaviour is noted in both sets. (Again, a line corresponding to another stable equilibrium $y^* = 0$ is not shown in these logarithmic plots.) The difference in the two approaches is less dramatic when no allowance is made for immigration and emigration of schistosomes.

Figures V-1 to V-9: Graphical study of critical points in years 1967, 1969 to 1976. The solid line is the plot of W^*_b, the dotted (.....), dashed (-------) and dot-dashed (•-•-•) lines those of W^*_a in the "together", "separate" and "Poisson" situations respectively.

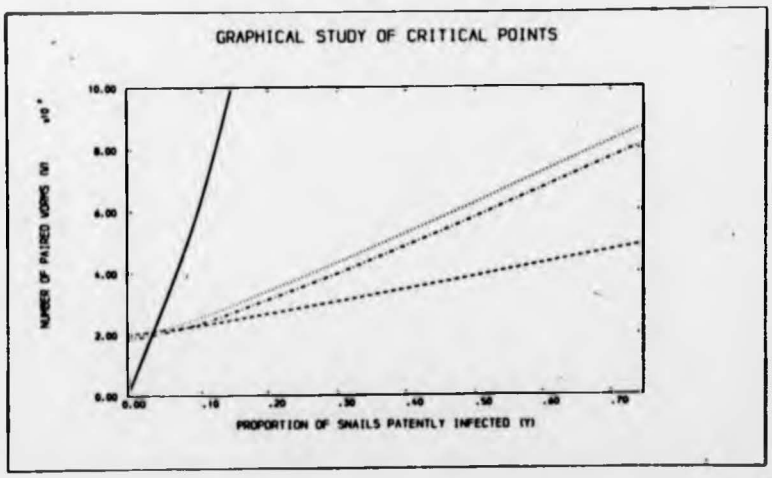
1967

FIGURE V-1



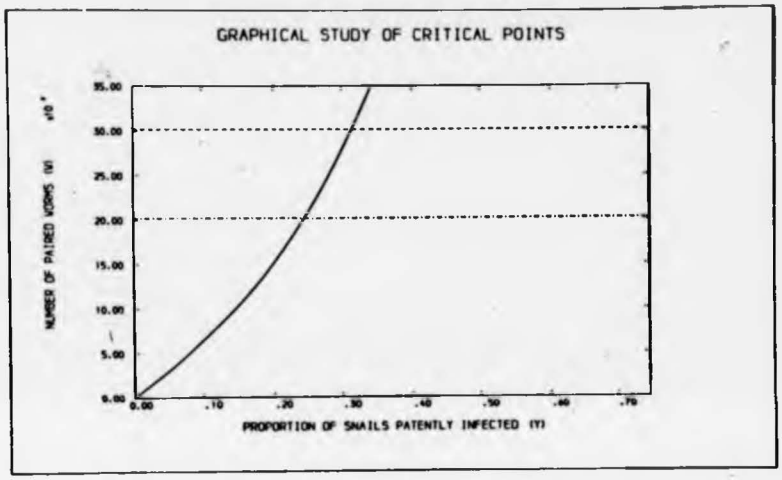
1969

FIGURE V-2



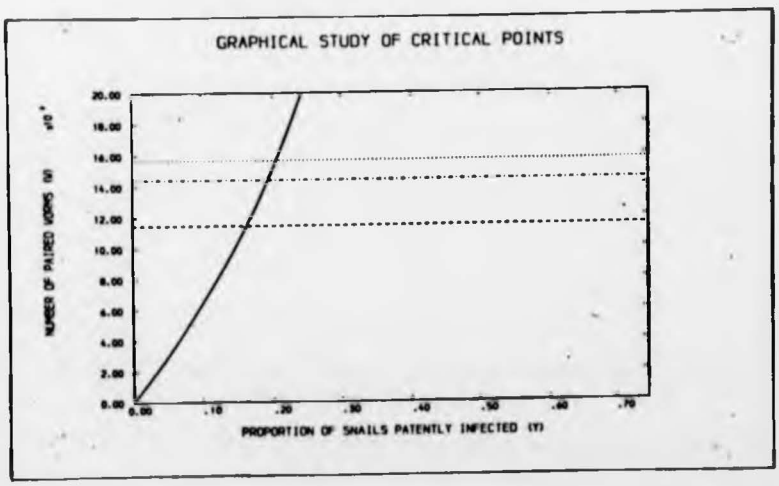
1970

FIGURE V-3



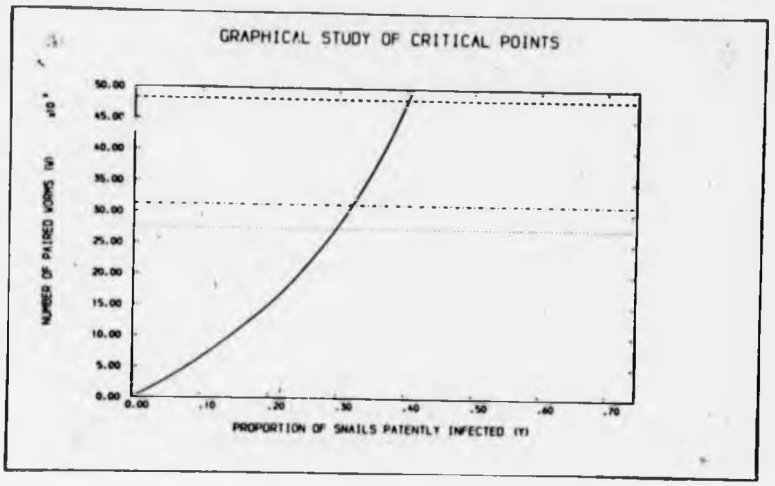
1971

FIGURE V-4



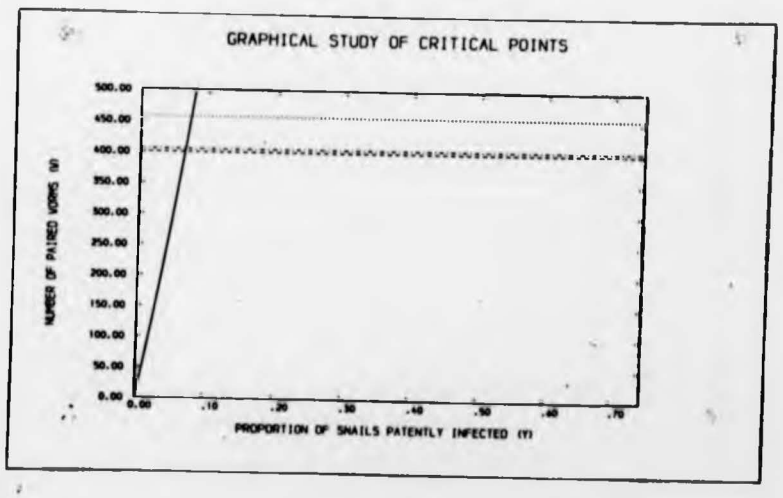
1972

FIGURE V-5



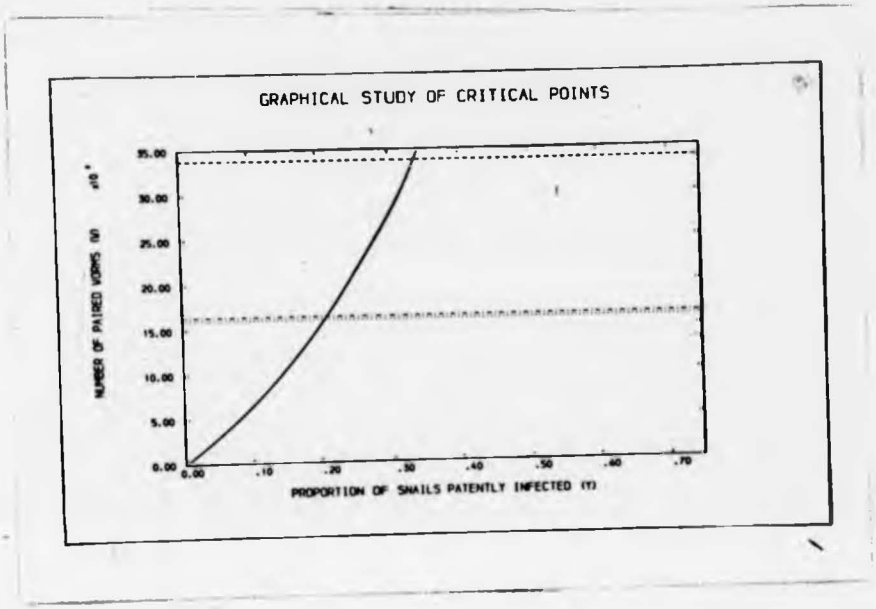
1973

FIGURE V-6



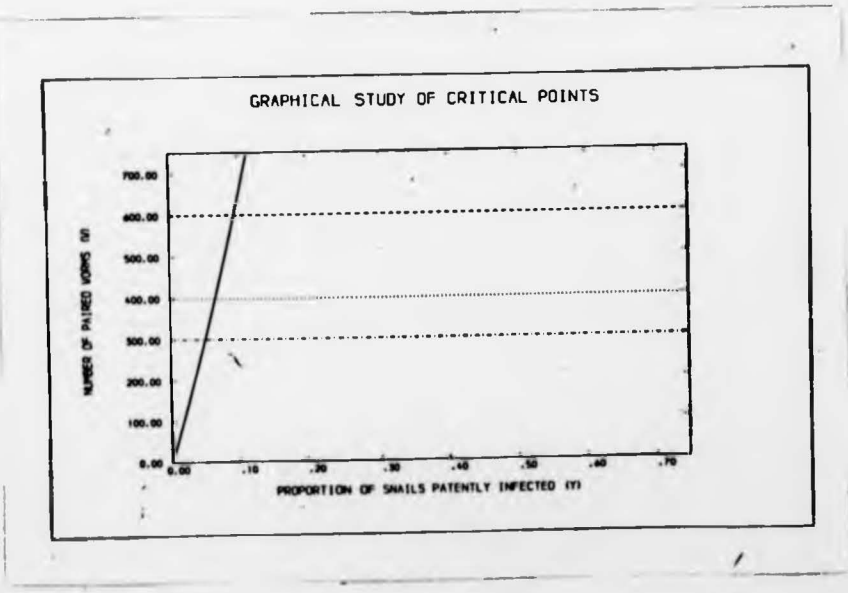
1974

FIGURE V-7



1975

FIGURE V-8



1976

FIGURE V-9

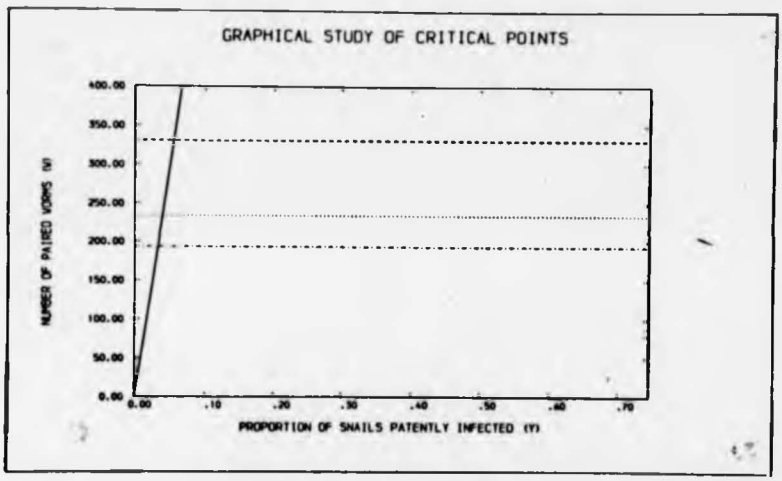


Figure V-10

Sensitivity of equilibrium proportion of patently infected snails (y*) to changes in snail number (N_2) for various changes in Schistosome longevity ($1/\mu_1$) when pairing follows the "together" situation (for 1967).

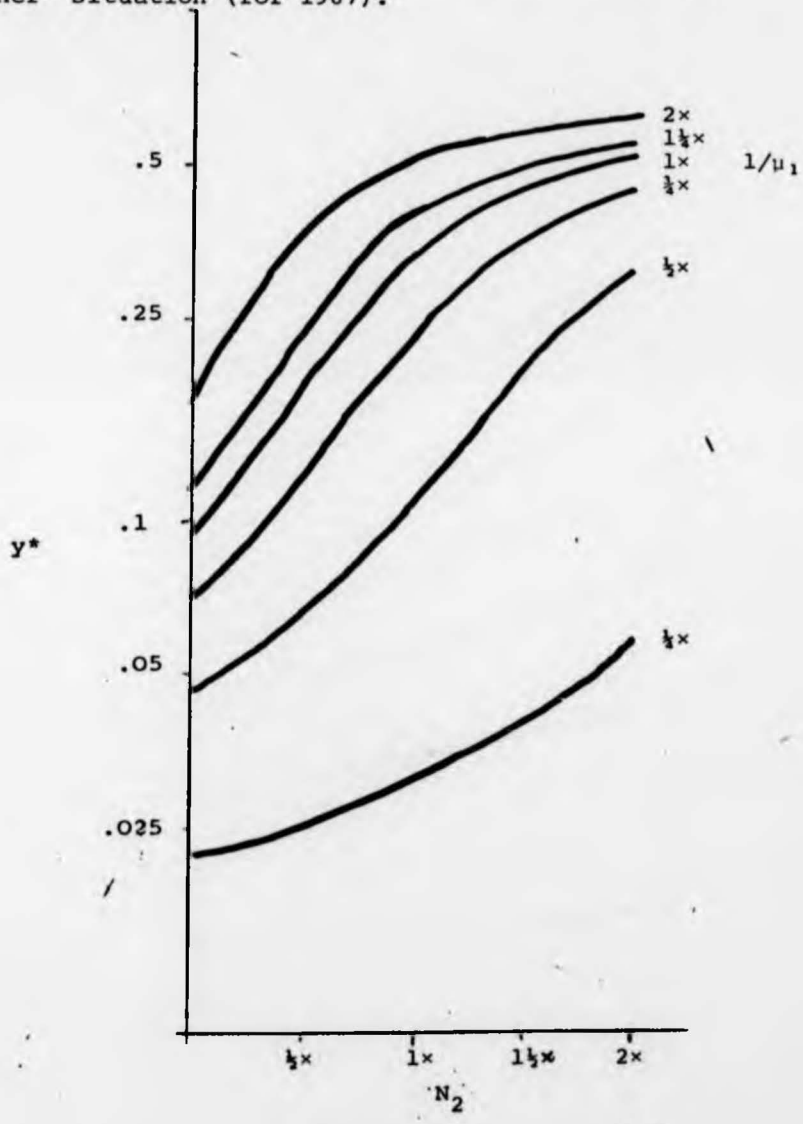


Figure V-11

As Figure V-10 in "separate" pairing situation.

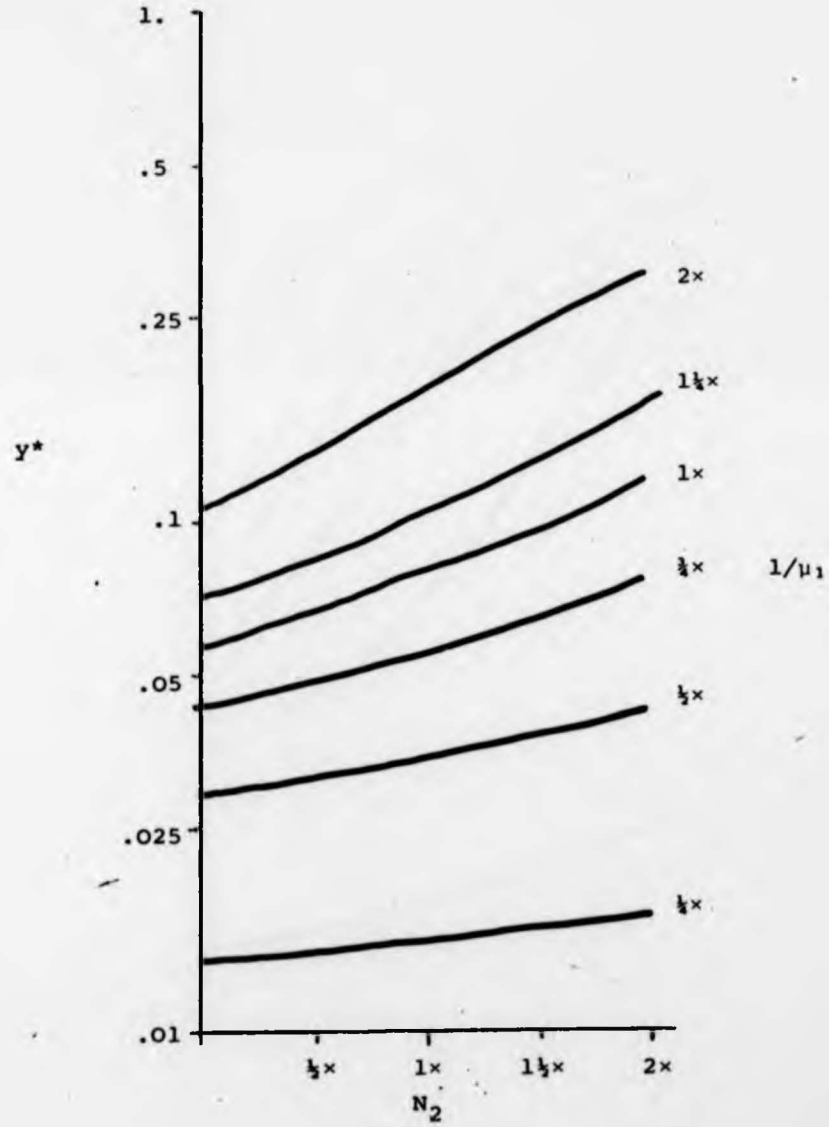


Figure V-12

As Figure V-10 in "Poisson" pairing situation.

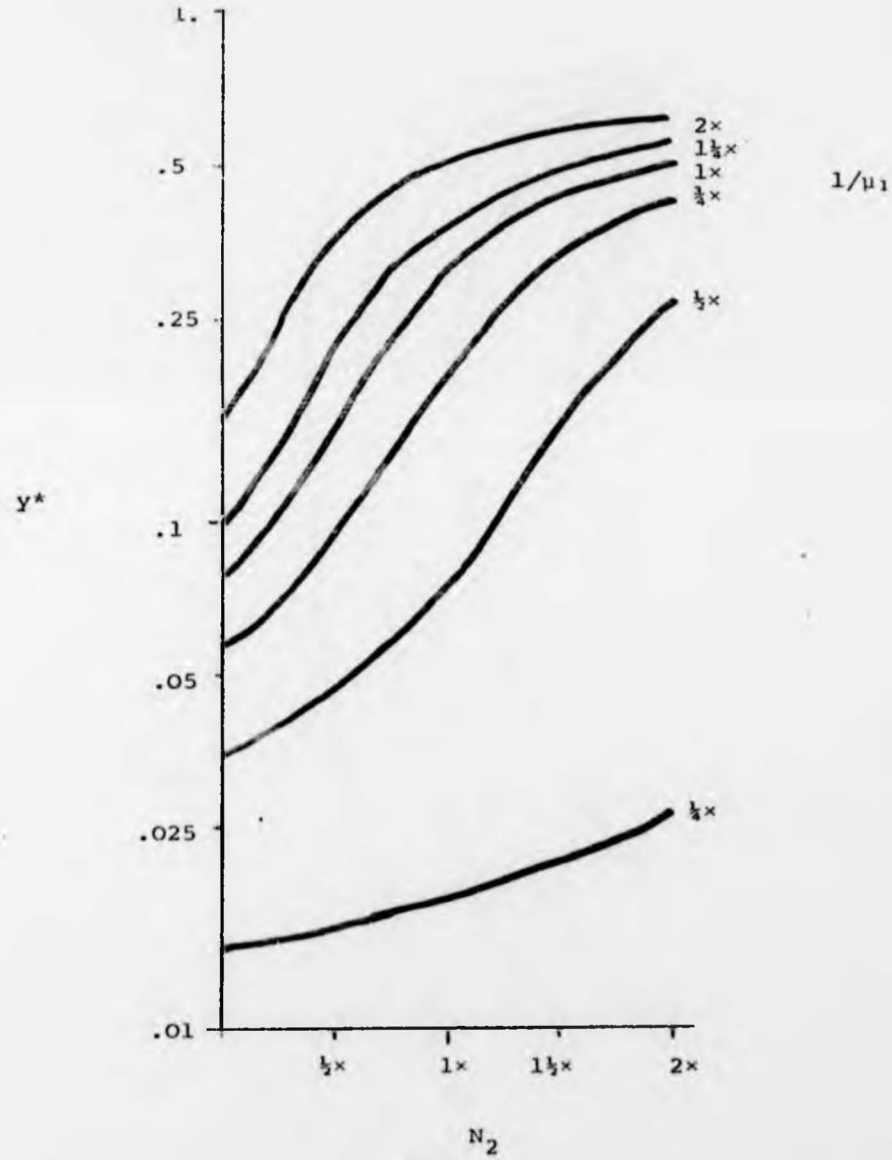


Figure V-13

As Figure V-10 with no consideration of immigration or emigration of worms. Pairing assumed to follow "together" situation. Solid lines denote stable equilibrium values, broken lines represent unstable equilibrium values (breakpoint). A line corresponding to $y^*=0$ is not shown on this plot.

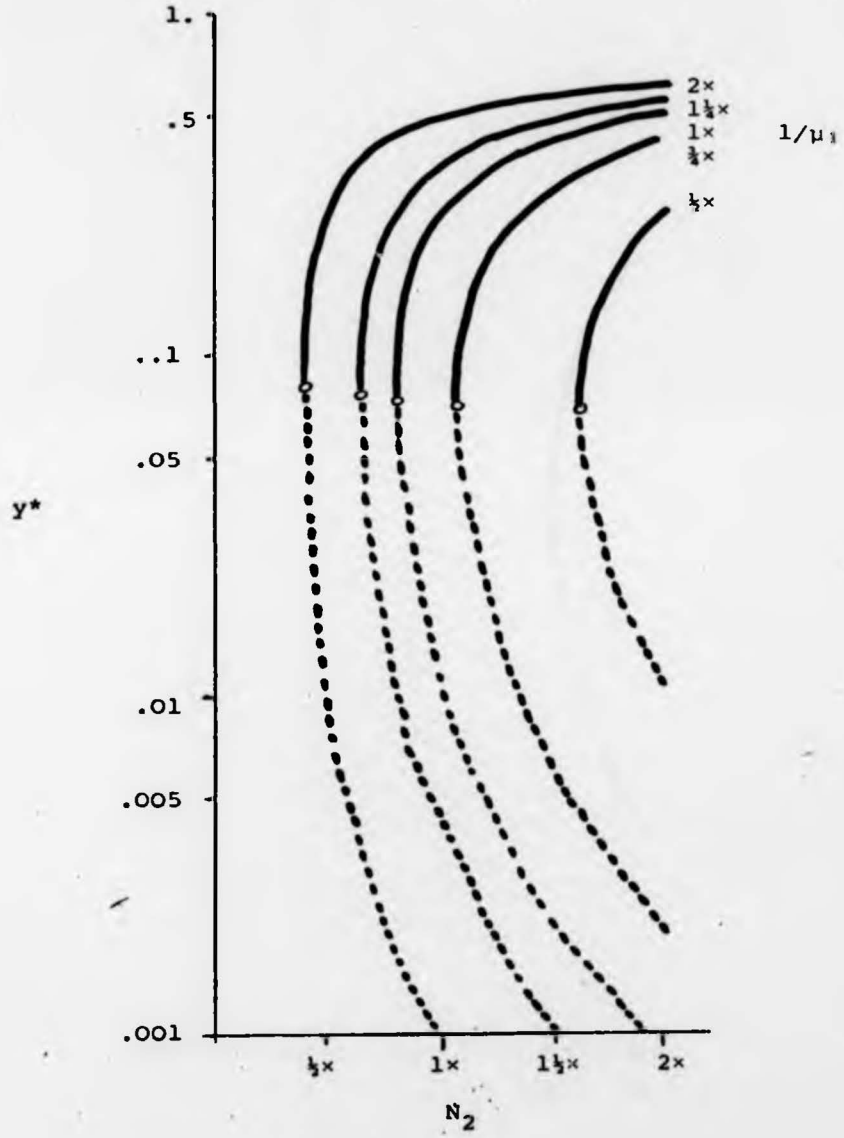


Figure V-14

As Figure v-13 in "separate" pairing situation.

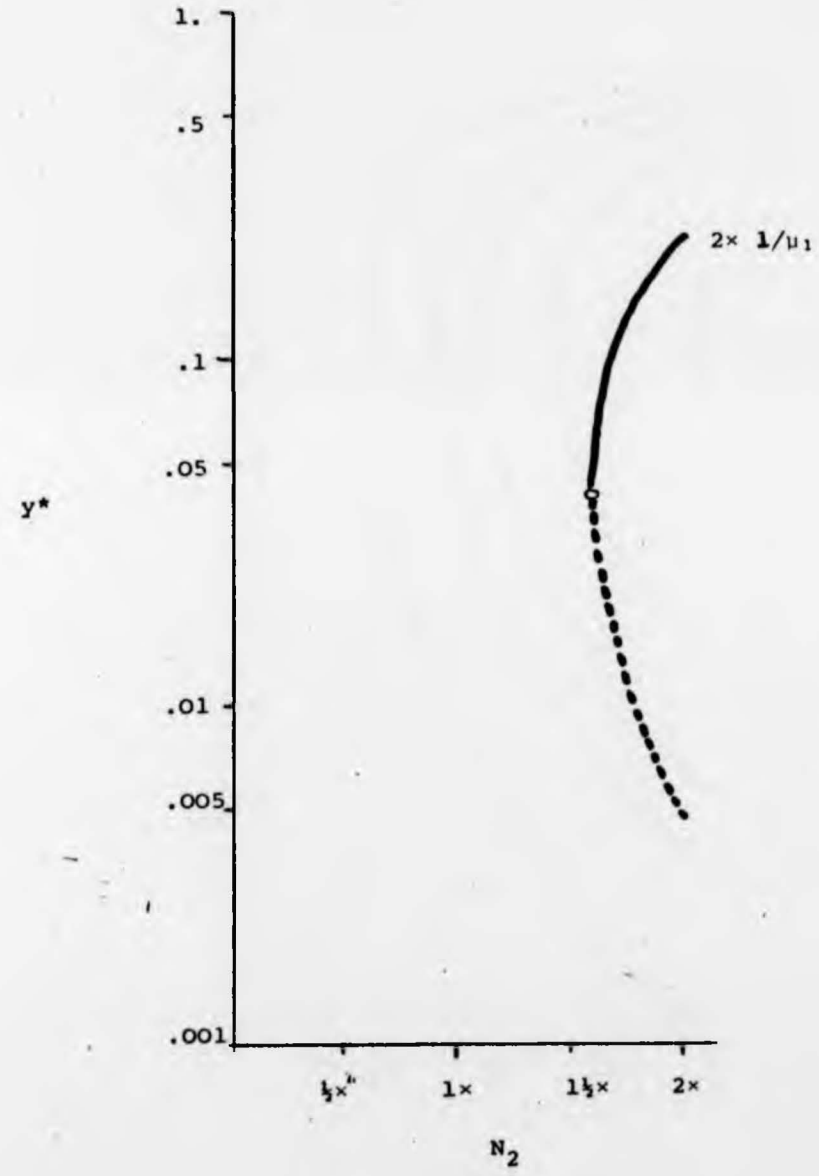


Figure V-15

As Figure V-13 in "Poisson" pairing situation.

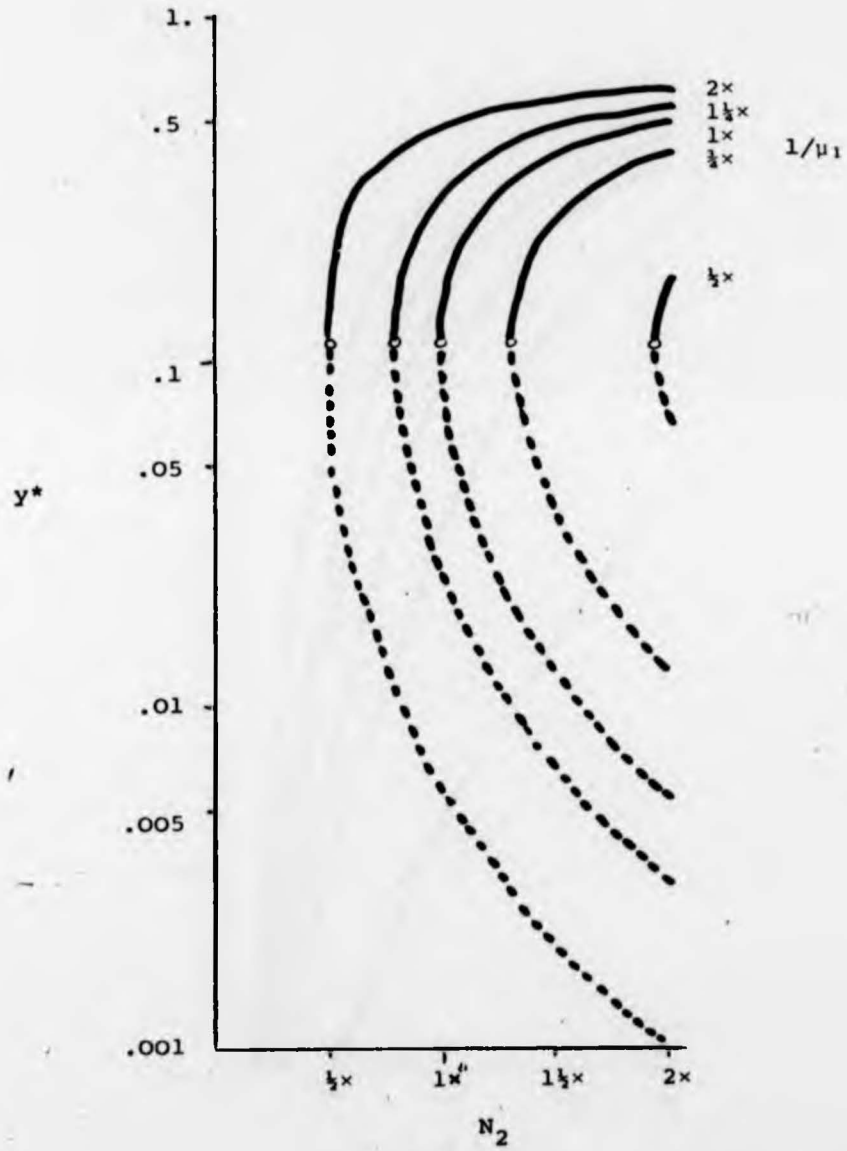


Figure V-16

Compare to Figure V-10. Changes in snail population modelled by altering μ_2' and μ_2'' rather than N_2. "Together" pairing situation.

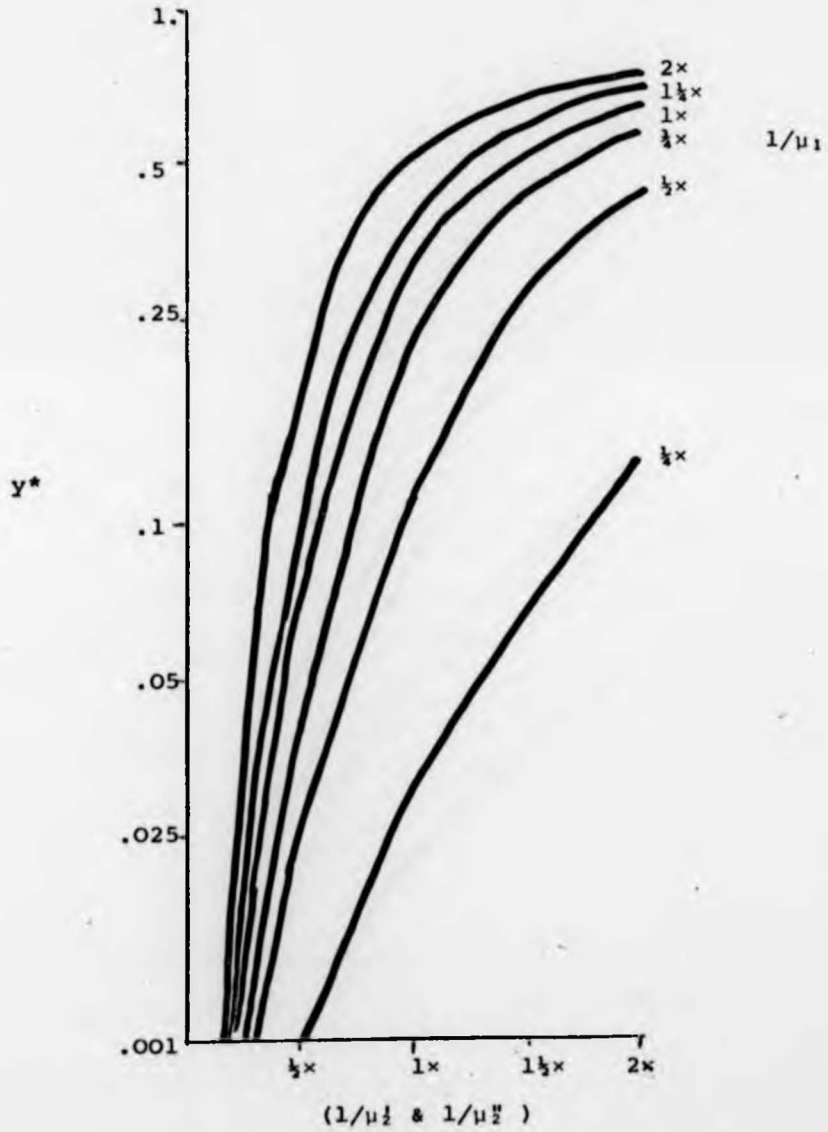


Figure V-17

As Figure V-16 in "separate" pairing situation. Compare to Figure V-11.

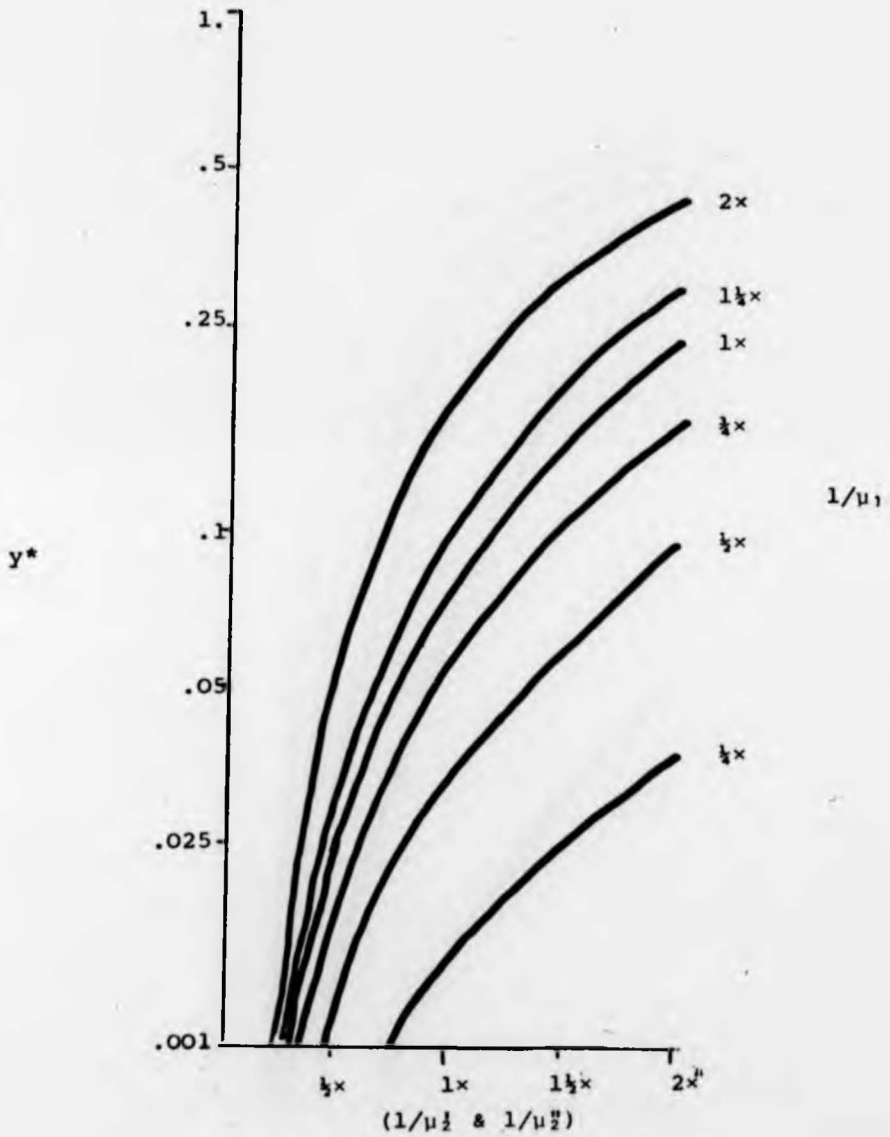


Figure V-18

As Figure V-16 in "Poisson" pairing situation. Compare to Figure V-12.

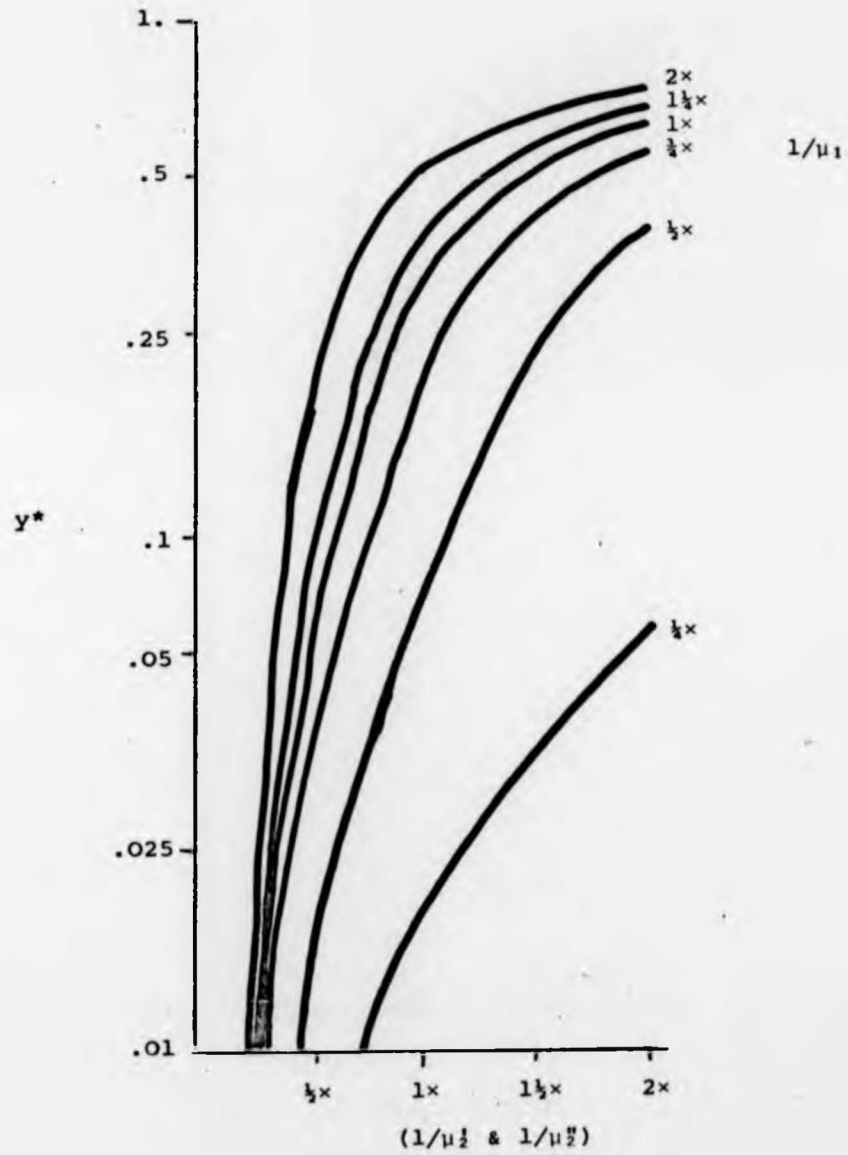


Figure V-19

Compare to Figure V-13. Changes in snail population modelled by altering μ_2' and μ_2'' rather than N_2. "Together" pairing situation.

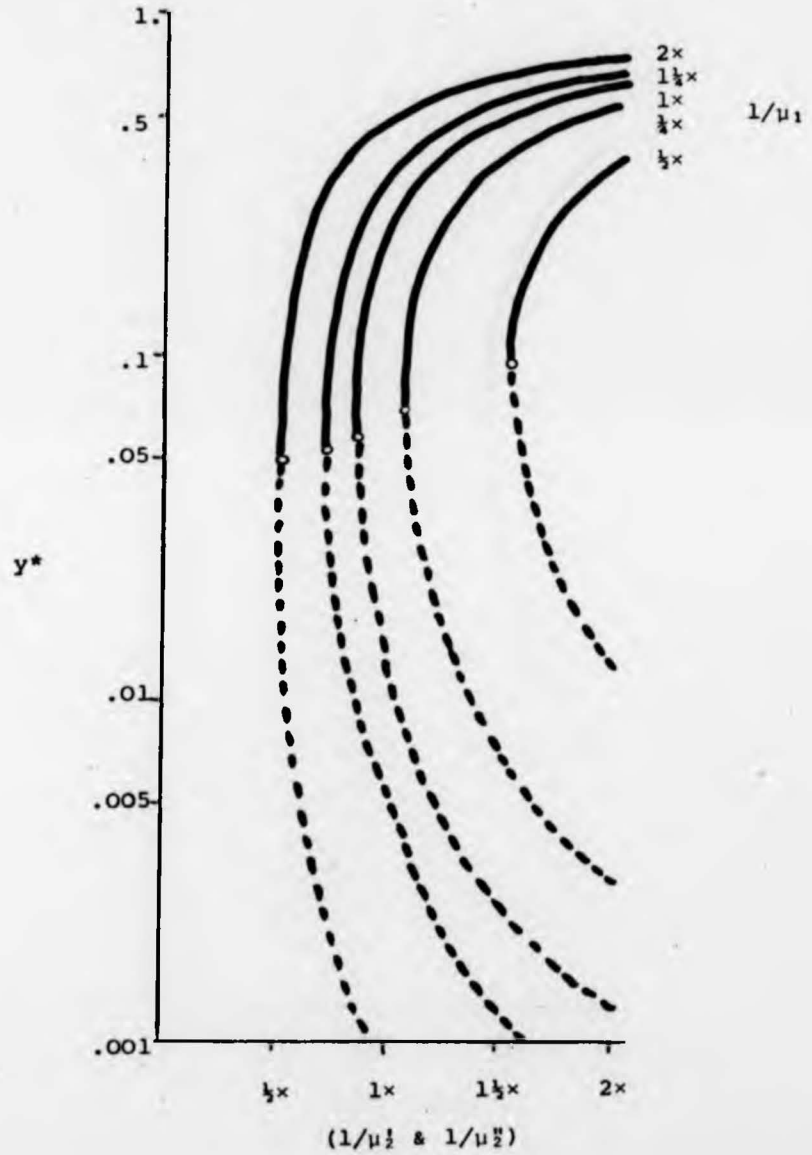


Figure V-20

As Figure V-19 in "Separate" pairing situation. Compare to Figure V-14.

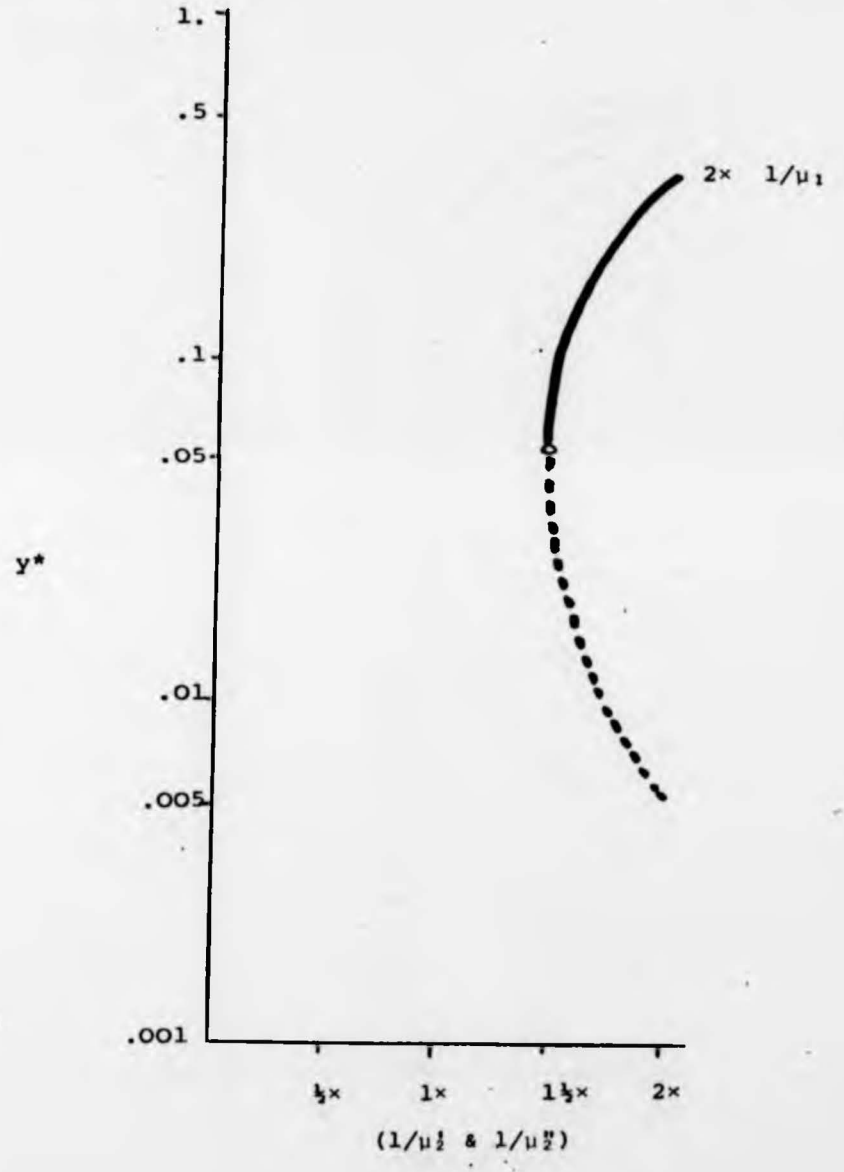


Figure V-21

As Figure V-19 in "Poisson" pairing situation. Compare to Figure V-15.

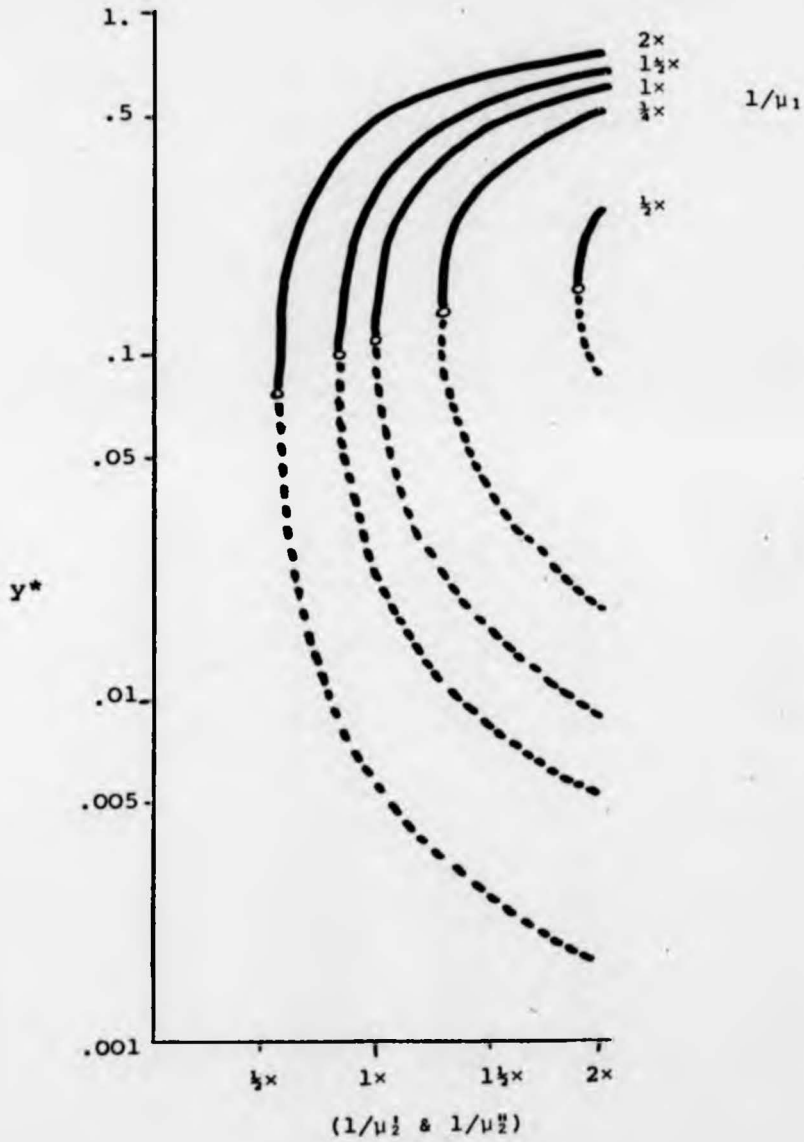


Table V-1

Predicted Mean Worm Load and Proportion of Snails Patent

1967-1969 (548 days)

* No immigration/emigration δ_i, $\varepsilon_i = 0$

Together

Variable	Start	End	End*	Observed	Deviation
m_1	2.0	1.4	1.0	8.8	7.4
m_2	28.0	16.0	16.0	10.6	-5.4
m_3	311.4	169.6	164.9	192.2	22.6
m_4	94.2	79.6	77.3	71.6	-8.0
m_5	30.8	52.0	53.7	28.8	-23.2
m_6	65.0	62.3	61.4	39.6	-22.7
m_7	7.8	15.3	15.2	10.8	-4.5
m_8	5.6	17.3	17.2	10.8	-6.5
m_9	0.0	28.6	28.5	0	-28.6
y	.0050	.5208	.5177	.0025	-.5181

Separate

m_1	8.4	4.4	3.7	20.2	15.8
m2	124.4	64.8	66.0	23.4	-41.4
m3	1449.0	757.0	745.3	487.4	-269.6
m_4	432.6	321.6	316.3	173.6	-148.0
m5	137.0	192.2	199.8	66.8	-125.4
m6	296.4	177.8	179.2	94.0	-83.8
m7	32.8	38.1	38.5	23.4	-14.7
m8	23.8	27.5	27.5	23.4	-4.1
m9	0	28.1	28.1	0	-28.1
y	.0050	.5008	.4998	.0025	-.4983

Poisson

m_1	2.2	1.5	1.1	9.2	7.7
m_2	30.2	17.2	17.1	11.4	-5.8
m_3	319.2	173.8	169.0	195.4	21.6
m_4	97.6	81.8	79.5	73.6	-8.2
m_5	33.0	53.9	55.7	30.2	-23.7
m_6	67.8	63.7	62.7	41.2	-22.5
m_7	8.8	15.9	15.9	11.8	-4.1
m_8	6.4	17.7	17.6	11.8	-5.9
m_9	0	28.6	28.5	0	-28.6
y	.0050	.5181	.5152	.0025	.5156

Table V-1 (contd.)

1969-1970

Variable	Start	End	End*	Observed	Deviation
Together					
m_1	8.8	4.8	4.7	3.6	-1.2
m_2	10.6	6.5	6.6	7.2	0.7
m_3	192.2	111.9	112.0	82.4	-29.5
m_4	71.6	65.7	72.0	101.0	35.3
m_5	28.8	37.2	34.7	40.2	3.0
m_6	39.6	29.3	29.3	33.0	3.7
m_7	10.8	7.7	7.7	10.8	3.1
m_8	10.8	8.4	8.4	10.8	2.4
m_9	0	4.0	4.1	0	-4.0
y	.0025	-	-	-	-
Separate					
m_1	20.2	10.9	10.9	8.0	-2.9
m_2	23.4	14.2	14.5	15.8	1.6
m_3	487.4	282.4	282.5	204.0	-78.4
m_4	173.6	161.3	176.7	250.6	89.3
m_5	66.8	87.2	81.3	96.0	8.8
m_6	94.0	67.0	67.0	78.0	11.0
m_7	23.4	16.1	16.1	23.4	7.3
m_8	23.4	17.1	17.1	23.4	6.3
m_9	0	6.5	6.5	0	-6.5
y	.0025	-	-	-	-
Poisson					
m_1	9.2	5.0	5.0	4.0	-1.0
m_2	11.4	6.9	7.0	7.6	0.7
m_3	195.4	114.0	114.0	84.6	-29.4
m_4	73.6	67.2	73.6	103.4	36.2
m_5	30.2	38.6	36.0	41.8	3.2
m_6	41.2	30.4	30.4	34.6	4.2
m_7	11.8	8.4	8.4	11.8	3.4
m_8	11.8	9.0	9.0	11.8	2.8
m_9	0	4.2	4.3	0	-4.2
y	.0025	-	-	-	-

Table V-1 (contd.)

1970-1971

Variable	Start	End	End*	Observed	Deviation
Together					
m_1	3.6	2.2	2.2	.6	-1.6
m_2	7.2	4.6	4.8	19.6	15.0
m_3	82.4	55.0	51.5	45.4	-9.6
m_4	101.0	75.3	67.4	94.4	19.1
m_5	40.2	43.1	36.2	32.8	-10.3
m_6	33.0	29.8	25.6	21.0	-8.8
m_7	10.8	9.8	9.1	10.2	0.4
m_8	10.8	6.9	6.9	12.0	5.1
m_9	0	1.3	1.3	0	-1.3
Separate					
m_1	8.0	4.8	4.8	2.0	-2.8
m_2	15.8	10.1	10.4	68.8	58.7
m_3	204.0	140.4	127.3	155.6	15.2
m_4	250.6	195.2	167.2	333.0	137.8
m_5	96.0	112.4	87.4	111.8	-0.6
m_6	78.0	75.4	60.8	69.8	-5.6
m_7	23.4	22.2	20.1	32.8	10.6
m_8	23.4	15.0	15.0	38.2	23.2
m_9	0	2.8	2.8	0	-2.8
Poisson					
m_1	4.0	2.4	2.4	.6	-1.8
m_2	7.6	4.9	5.0	20.4	15.5
m_3	84.6	56.5	52.9	47.8	-8.7
m_4	103.4	77.2	69.1	97.8	20.6
m_5	41.8	44.7	37.4	34.8	-9.9
m_6	34.6	31.2	26.8	22.6	-8.6
m_7	11.8	10.6	9.9	11.4	0.8
m_8	11.8	7.6	7.6	13.4	5.8
m_9	0	1.4	1.4	0	-1.4

Table V-1 (contd.)

1971-1972

Variable	Start	End	End*	Observed	Deviation
Together					
m_1	.6	.8	.4	1.0	0.2
m_2	19.6	12.5	12.4	8.4	-4.1
m_3	45.4	35.6	27.2	30.6	-5.0
m_4	94.4	62.0	60.8	92.8	30.8
m_5	32.8	35.4	33.7	37.6	2.2
m_6	21.0	14.5	13.8	15.4	0.9
m_7	10.2	6.9	6.9	17.8	10.9
m_8	12.0	7.6	7.6	14.6	7.0
m_9	0	2.0	2.0	6.2	4.2
Separate					
m_1	2.0	2.1	1.3	2.2	0.1
m_2	68.8	43.7	43.4	18.2	-25.5
m_3	155.6	114.1	93.3	70.8	-43.3
m_4	333.0	216.7	213.8	219.4	2.7
m_5	111.8	119.3	116.1	85.2	-34.1
m_6	69.8	47.5	46.0	33.0	-14.5
m_7	32.8	22.3	22.2	38.2	15.9
m_8	38.2	24.1	24.1	31.0	6.9
m_9	0	6.3	6.3	12.0	5.7
Poisson					
m_1	.6	.8	.4	1.0	0.2
m_2	20.4	13.0	12.9	9.0	-4.0
m_3	47.8	37.1	28.6	31.6	-5.5
m_4	97.8	64.3	63.2	95.0	30.7
m_5	34.8	37.3	35.5	39.0	1.7
m_6	22.6	15.6	14.8	16.6	1.0
m_7	11.4	7.6	7.6	18.8	11.2
m_8	13.4	8.4	8.4	15.6	7.2
m_9	0	2.2	2.2	6.8	4.6

Table V-1 (contd.)

1972-1973

Together

Variable	Start	End	End*	Observed	Deviation
m_1	1.0	.5	.5	.4	-0.1
m_2	8.4	5.1	4.7	7.0	1.9
m_3	30.6	20.1	21.2	17.0	-3.1
m_4	92.8	69.8	59.4	68.4	-1.4
m_5	37.6	32.1	25.8	36.8	4.7
m_6	15.4	10.5	10.9	14.0	3.5
m_7	17.8	12.4	10.7	19.6	7.2
m_8	14.6	16.5	12.8	20.2	3.7
m_9	6.2	6.5	5.3	24.0	17.5

Separate

m_1	2.2	1.1	1.2	1.6	0.5
m_2	18.2	11.8	10.3	23.2	11.4
m_3	70.8	47.3	48.7	55.6	8.3
m_4	219.4	191.1	140.3	236.4	45.3
m_5	85.2	87.1	58.9	123.4	36.3
m_6	33.0	23.1	23.6	46.2	23.1
m_7	38.2	29.1	22.9	65.6	36.5
m_8	31.0	39.8	27.2	66.0	26.2
m_9	12.0	58.7	10.4	80.2	21.5

Poisson

m_1	1.0	.5	.5	.6	0.1
m_2	9.0	5.4	5.1	7.6	2.2
m_3	31.6	20.9	21.9	18.4	-2.5
m_4	95.0	71.4	60.8	71.0	-0.4
m_5	39.0	33.2	26.7	39.0	5.8
m_6	16.6	11.3	11.7	15.2	3.9
m_7	18.8	13.2	11.3	20.8	7.6
m_8	15.6	17.6	13.6	21.6	4.0
m_9	6.8	20.5	5.7	25.6	5.1

Table V-1 (contd.)

1973-1974

Variable	Start	End	End*	Observed	Deviation
Together					
m_1	.4	.2	.2	0	-.2
m_2	7.0	3.6	3.9	1.2	-2.4
m_3	17.0	10.5	11.2	24.6	14.1
m_4	68.4	39.1	41.0	58.6	19.5
m_5	36.8	26.1	30.9	43.6	17.5
m_6	14.0	15.4	14.1	24.0	8.6
m_7	19.6	13.3	13.5	7.6	-5.7
m_8	20.2	14.6	14.4	22.4	7.8
m_9	24.0	15.8	17.3	17.4	1.6
Separate					
m_1	1.6	.8	.8	0	-.8
m_2	23.2	11.9	13.1	3.0	-8.9
m_3	55.6	34.5	36.7	66.6	32.1
m_4	236.4	132.9	141.3	157.8	24.9
m_5	123.4	86.9	104.3	114.8	27.9
m_6	46.2	49.6	46.8	62.0	12.4
m_7	65.6	44.3	45.1	17.6	-26.7
m_8	66.0	47.3	47.3	58.0	10.7
m_9	80.2	52.7	57.7	43.8	-8.9
Poisson					
m_1	.6	.3	.3	0	-.3
m_2	7.6	3.9	4.3	1.2	-2.7
m_3	18.4	11.4	12.1	25.6	14.2
m_4	71.0	40.7	42.7	61.0	20.3
m_5	39.0	27.5	32.5	45.6	18.1
m_6	15.2	16.6	15.2	25.6	9.0
m_7	20.8	14.2	14.3	8.4	-5.8
m_8	21.6	15.6	15.4	23.8	8.2
m_9	25.6	16.9	18.4	18.8	1.9

Table V-1 (contd.)

1974-1975

Together

Variable	Start	End	End*	Observed	Deviation
m_1	0	0	0	.6	.6
m_2	1.2	.8	.7	.2	-.6
m_3	24.6	13.3	14.0	19.6	6.3
m_4	58.6	39.1	40.3	26.4	-12.7
m_5	43.6	32.9	30.7	27.2	-5.7
m_6	24.0	24.6	23.3	16.8	-7.8
m_7	7.6	8.0	5.6	4.8	-3.2
m_8	22.4	19.5	14.3	27.4	7.9
m_9	17.4	16.8	14.4	14.6	-2.2

Separate

m_1	0	0	0	3.4	3.4
m_2	3.0	2.5	1.7	1.2	-1.3
m_3	66.6	36.1	37.9	105.4	69.3
m_4	157.8	106.9	108.5	140.2	33.3
m_5	114.8	105.4	81.0	142.8	37.4
m_6	62.0	68.8	60.6	89.4	20.6
m_7	17.6	28.1	13.1	25.2	-2.9
m_8	58.0	67.5	36.9	147.2	79.7
m_9	43.8	52.3	36.3	76.2	23.9

Poisson

m_1	0	0	0	.8	.8
m_2	1.2	.9	.7	.2	-.7
m_3	25.6	13.9	14.6	21.0	7.1
m_4	61.0	40.8	41.9	28.6	-12.2
m_5	45.6	34.6	32.1	29.8	-4.8
m_6	25.6	26.2	24.7	18.4	-7.8
m_7	8.4	8.7	6.2	5.2	-3.5
m_8	23.8	20.8	15.2	29.4	8.6
m_9	18.8	18.4	15.5	16.2	-2.2

Table V-1 (cont.)

1975-1976

Variable	Start	End	End*	Observed	Deviation
Together					
m_1	.6	.3	.3	0	-.3
m_2	.2	.6	.2	1.4	0.8
m_3	19.6	11.5	11.7	2.4	-9.1
m_4	26.4	15.5	17.3	3.4	-12.1
m_5	27.2	18.2	20.1	10.2	-8.0
m_6	16.8	13.8	14.4	.4	-13.4
m_7	4.8	4.1	4.0	1.4	-2.7
m_8	27.4	18.0	18.6	0	-18.0
m_9	14.6	10.0	11.0	2.4	-7.6
Separate					
m_1	3.4	1.6	1.7	0	-1.6
m_2	1.2	4.1	1.0	9.0	4.9
m_3	105.4	62.5	63.2	16.2	-46.3
m_4	140.2	82.3	92.0	22.8	-59.5
m_5	142.8	99.9	105.6	68.4	-31.5
m_6	89.4	73.7	76.3	2.4	-71.3
m_7	25.2	21.8	20.9	9.4	-12.4
m_8	147.2	96.6	99.9	0	-96.6
m_9	76.2	52.5	57.3	16.6	-35.9
Poisson					
m_1	.8	.4	.4	0	-.4
m_2	.2	.7	.2	1.6	0.9
m_3	21.0	12.4	12.6	2.8	-9.6
m_4	28.6	16.7	18.7	4.2	-12.5
m_5	29.8	19.9	21.9	11.6	-8.3
m_6	18.4	15.1	15.7	.4	-14.7
m_7	5.2	4.5	4.3	1.8	-2.7
m_8	29.4	19.3	20.0	0	-19.3
m_9	16.2	11.1	12.1	3.0	-8.1

Table V-1 (cont.)

1976-1977

Together

Variable	Start	End	End*	Observed	Deviation
m_1	0	0	0	0	0
m_2	1.4	.7	.8	0	-.7
m_3	2.4	1.5	1.7	.2	-1.3
m_4	3.4	1.9	2.4	2.6	.7
m_5	10.2	7.9	7.0	3.6	-4.3
m_6	.4	.6	.7	0	-.6
m_7	1.4	.7	.8	.8	.1
m_8	0	.1	.1	.6	.5
m_9	2.4	1.6	1.7	0	-1.6

Separate

m_1	0	0	0	0	0
m_2	9.0	4.4	4.9	0	-4.4
m_3	16.2	9.9	11.2	2.0	-7.9
m_4	22.8	12.5	16.0	23.0	10.5
m_5	68.4	57.7	47.1	32.0	-25.7
m_6	2.4	4.1	4.2	0	-4.1
m_7	9.4	4.6	5.4	6.8	2.2
m_8	0	.8	.9	4.8	4.0
m_9	16.6	11.1	11.6	0	-11.1

Poisson

m_1	0	0	0	0	0
m_2	1.6	.8	.9	0	-.8
m_3	2.8	1.7	1.9	.2	-1.5
m_4	4.2	2.3	2.9	3.6	1.3
m_5	11.6	8.9	8.0	4.0	-4.9
m_6	.4	.7	.7	0	-.7
m_7	1.8	.9	1.0	1.0	.1
m_8	0	.2	.2	.6	.4
m_9	3.0	2.0	2.1	0	-2.0

Table V-2 Equilibrium Values

1967-1969

	Together	Separate	Poisson
m_1	1.0	1.7	1.0
m_2	3.7	3.7	3.6
m_3	19.6	27.0	18.9
m_4	23.3	17.5	21.9
m_5	33.2	15.3	30.6
m_6	49.1	25.5	45.6
m_7	20.1	7.7	18.6
m_8	27.0	6.3	24.6
m_9	55.0	12.8	50.1
x	.5443	.8940	.5848
y	.3403	.0792	.3101
z	.1154	.0268	.1051
w	3468.0	491.4	2941.0

1969-1970

	Together	Separate	Poisson
m_1	.01	.01	.01
m_2	.25	.50	.27
m_3	.30	.50	.31
m_4	.27	.35	.27
m_5	10.81	25.34	11.22
m_6	.70	.71	.67
m_7	.16	.16	.15
m_8	.30	.31	.29
m_9	.93	.93	.88
x	.9521	.9519	.9546
y	.0357	.0359	.0339
z	.0121	.0122	.0115
w	208.2	209.4	197.0

Table V-2 (cont.)

1970-1971

	Together	Separate	Poisson
m_1	0	0	0
m_2	0	0	0
m_3	11.57	40.14	12.08
m_4	21.81	77.18	22.54
m_5	26.01	90.16	27.22
m_6	18.91	65.56	19.80
m_7	5.21	17.63	5.55
m_8	0	0	0
m_9	0	0	C
w	2018.1	3013.9	2015.7

1971-1972

	Together	Separate	Poisson
m_1	1.06	2.31	1.13
m_2	.94	2.00	1.01
m_3	19.41	47.82	19.68
m_4	10.29	25.35	10.43
m_5	11.63	27.30	11.98
m_6	2.77	6.18	2.93
m_7	.46	1.03	.49
m_8	.04	.10	.05
m_9	.03	.07	.03
w	1566.8	1145.7	1440.9

Table V-2 (cont.)

1972-1973

	Together	Separate	Poisson
m_1	0	0	0
m_2	1.50	4.87	1.62
m_3	2.85	9.24	3.08
m_4	43.4	155.06	44.34
m_5	23.7	83.07	24.45
m_6	2.48	8.68	2.55
m_7	4.96	16.30	5.31
m_8	13.69	45.68	14.55
m_9	6.50	142.61	44.11
w	2744.6	4822.4	3127.2

1973-1974

	Together	Separate	Poisson
m_1	0	0	0
m_2	0	0	0
m_3	0	0	0
m_4	5.36	14.49	5.56
m_5	4.34	11.53	4.53
m_6	7.44	19.29	7.90
m_7	1.71	4.28	1.85
m_8	2.01	5.11	2.17
m_9	.20	.50	.21
w	456.9	400.2	405.1

Table V-2 (cont.)

1974-1975

	Together	Separate	Poisson
m_1	0	0	0
m_2	.40	2.00	.46
m_3	.14	.72	.17
m_4	1.56	8.05	1.74
m_5	14.32	75.92	15.50
m_6	11.86	62.05	13.13
m_7	7.76	41.18	8.40
m_8	15.49	82.69	16.62
m_9	14.14	72.70	16.00
w	1602.5	3378.4	1637.2

1975-1976

	Together	Separate	Poisson
m_1	0	0	0
m_2	.94	6.40	1.04
m_3	1.30	8.82	1.47
m_4	.38	2.55	.42
m_5	4.87	33.45	5.36
m_6	1.92	13.18	2.11
m_7	.95	6.21	1.16
m_8	.15	.97	.18
m_9	.01	.09	.02
w	397.4	600.1	299.5

Table V-2 (cont.)

1976-1977

	Together	Separate	Poisson
m_1	0	0	0
m_2	0	0	0
m_3	0	0	0
m_4	0	0	0
m_5	4.84	43.18	5.39
m_6	.55	4.88	.61
m_7	0	0	0
m_8	0	0	0
m_9	0	0	0
w	234.3	330.7	193.4

Chapter Six:- Conclusion

In this last section, an attempt is made to summarize the observations made in previous chapters, and draw some broad conclusions.

1) Summary

One might argue that the current trend in models for schistosomiasis began with a paper by Macdonald in 1965(a). The conclusions that Macdonald reached have influenced attitudes to control measures, but there is concern that some observations may have not been as general as Macdonald intended (Nåsell, 1977). The 1965 paper itself does not contain sufficient information to reproduce Macdonald's figures. As a starting point, it seemed appropriate to explore Macdonald's notes in the Ross Institute and critically appraise the model.

In Chapter Two a specific parameterization for the 1965 model was described. It was not possible to determine a specific value for each parameter mentioned, but there was sufficient information to recreate all of Macdonald's diagrams except his Figure 4. The inability to do this suggests that the suggested values of parameters may not be exactly those employed by Macdonald.

With these values, it was possible to study specific properties of the model which have been questioned. In Macdonald's "standard" situation, as well as under control conditions, the proportion of snails patently infected tends to be rather high. The similarity in effect of changes in Macdonald's exposure and snail factors has been traced to a mathematical assumption and does not greatly depend on parameter values.

The insensitivity of intensity of infection to changes in the contamination factor appears to result from the values of the parameters.

To facilitate the study of the asymptotic behaviour of Macdonald's model, a graphical technique was described. This provided a quick means to obtain the equilibrium mean worm load and breakpoint value. The approach provides a visual way to understand the breakpoint "washout" phenomenon and effects of relaxing the assumption that worms follow a Poisson distribution within the human host.

A recent adaptation of Macdonald's model has been extensively studied by Nåsell and Hirsch (1973). It was possible to introduce Macdonald's parameters in the Nåsell-Hirsch setting and confirm Nåsell's suspicion (1977) that relative insensitivity to contamination was parameter specific and not a general phenomenon. The Macdonald model was based on a one-dimensional differential system, while that of Nåsell and Hirsch was based on two dimensions. A visual check of the phase space between the proportion of snails patently infected and mean worm load suggested that for Macdonald's parameterization, the distinction was unimportant. Current feeling, however, is that the additional complications of including an extra degree of freedom are warranted for the added generality.

The Macdonald-Nåsell-Hirsch (MNH) model unfortunately predicts uniformly increasing intensity of infection with age in humans. Field data tend to be unimodal, however, with a maximum intensity in the teenage years. Epidemiologists have suggested at least two causes for the decline after the teenage peak: it is possibly due to an immune effect, or it is due to less exposure to infected water by older age groups. With the availa-

bility of exposure data, it seemed reasonable to adapt the MNH formulation and explore the consequences of allowing for age-dependent exposure.

In Chapter Three, a model was described which attempted to use age-dependent exposure data. There were several minor adaptations made to the MNH formulation, but the structure is not very different from that of MNH. The definitive host population was split into several categories each with different rates of exposure to infected water. The data to be incorporated later summarized exposure in nine age categories, and thus nine age groups of hosts were chosen, while alteration to any number of exposure categories is trivial. It was also expedient to incorporate some recent ideas for changes in the MNH model, and several described by May (1977) were used. The distribution of worms in hosts was permitted to be clumped, and allowance for the latent period of infection in snails was made by lagged differential equations. Lastly, not only because data were available, but also because it was easily incorporated, allowance was made for the immigration and emigration of worms to the human population.

The model was thus changed from a formal mathematical statement of assumptions and consequences (as in the Nåsell-Hirsch approach) to a more empirical vehicle. The clumping phenomenon described by Bradley and May (1978) is not justified mathematically from basic assumptions. Macdonald (1965b esp.p.615) mentions that failure to mathematically justify the log-normal distribution of egg output held up development of models for schistosomiasis. The incorporation of immigrations and emigrations as well as flows of infection between age groups was another attempt to improve the accuracy of the model's behaviour. So as not to end up with a purely empirical life table model, an asymmetry was

introduced in handling the inflow and losses of worms to any age group. The actual worm load of immigrating definitive hosts was assumed known while the worm load of emigrating humans was taken to be that predicted and not that recorded. It was felt that the parameters introduced, though numerous, were more readily obtainable, while those remaining from the MNH situation remained the far more difficult to obtain.

The asymptotic behaviour of the system was briefly studied. The conditions of existence of one, two or three equilibrium states were studied, and a graphical technique described. By studying the intersections of two curves on a plot of the asymptotic proportion of snails patently infected (y^*) and the asymptotic total paired worm load (W^*) in a community, one could establish how many equilibrium states there were. It was suggested that whereas mean worm load has formerly been a criterion for studying the behaviour of a model, the proportion of snails patently infected (y^*) might be considered. This was recommended as, firstly, it was immaterial which variable is chosen. Secondly, as this type of model frequently predicted large proportions of infected snails, this approach put a suspect result in open view and did not discreetly hide it. The graphical approach again facilitated the display of the breakpoint "washout" at higher transmission levels. This can occur when there is sufficient immigration to override the pairing effect. While the complexity of the model (both through multiple exposure categories and complicated pairing functions) precluded algebraic solution to determine the values of y^* for a set of parameters, a numerical algorithm based on the graphical method to determine the possible values of y^* was described. Once the set of y^* has been

determined, all other variable values could be readily calculated by substitution.

In order to assess the behaviour of the model of Chapter Three in the field, parameters were estimated in Chapter Four. The area under consideration is part of the Cul de Sac valley in St Lucia, called Ravine Poisson. After a brief description of the village and the available records, each parameter described in the previous chapter was determined.

In attempting to describe a fairly complicated transmission pattern by means of such a crude model, on several occasions an assumption of homogeneity or constancy was made. The validity of this type of assumption is frequently excused by conveniently assuming that the effects of any deviation are "averaged out" when the constancy (and possibly even the distribution) of the snail population is considered.

Human populations were fairly readily estimated while the calculation of worm loads was fraught with assumptions. Most of these drawbacks apply to the MNH model, independent of the adaptations made here. One point is relevant to this data set, however. While the records of infection obtained by Research and Control are as complete as could be expected it is obviously infeasible to expect that each member of the community could be annually tested for level of infection. And while it was possible to separate out people with missing observations into those contributing to transmission during a period and those not, it was also necessary to estimate the level of infection in the former cases. This necessitated a missing value technique, and that chosen is clearly inconsistent with the model to which the data would subsequently be

applied. Future considerations may benefit by a more appropriate approach, but the approach used here was justified by claiming that the level of inexactitude was in keeping with other crude parameter estimations.

The estimation of parameters involved in the transmission of infection from snail to human involved use of exposure data from an area outside Ravine Poisson. It was hypothesized that inclusion of age-dependent exposure would produce age intensity of infection curves similar to those found in the field. While one could guage the appropriateness of this merely by visually comparing the two curves, the use of a model permitted other parameters to affect the relation between the two curves. The data used came from another area and were based only on observations of females, largely representing exposure for bathing and washing items. The generality of any model based observations is obviously restricted by this.

Throughout the exercise of obtaining parameter estimates, comparisons were made where possible with values used by Macdonald (1965a) and Hairston (1965). There were no great discrepancies with the possible exception of the death rates of snails. May (1977) has pointed out that the advantages of using a two dimensional systems will be greater when μ_1, μ_2' and μ_2'' are not similar, and the small values of μ_2' and μ_2'' employed here recommend letting snail infection rates vary dynamically. In some instances, the similarity of values developed independently by Hairston and Macdonald is striking.

While parameters are derived in Chapter Four, their appropriateness is

discussed in the first part of the fifth chapter. No confidence limits are provided for the parameters (except those for pairing) and at each step, one is reminded of the crude nature of values employed. The model is not employed as an ultimate attempt to explain transmission, but rather as a tool to roughly examine the consequences of age dependent exposure on transmission.

For each year studied, values of the variables for the next survey were predicted and compared with observed results. The proportion of snails patently infected constantly exceeded observed values by large amounts. This is clear evidence that another factor warrants consideration before the model could be said to produce realistic results. The intensity of infection in human hosts fared much better, and while not producing predictions that strikingly agree with values observed, they were generally not as grossly erroneous as the snail results. Predictions were not consistently above or below observed values. The dependence of the predictions on flows of worms through emigration and immigration was studied as well. The predictions varied little from those admitting these flows, and it was concluded that predicted infection arose mostly from retained or internally transmitted infection.

The equilibrium situation for each of the nine inter-survey periods was studied. Again, the proportions of snails infected appeared to be much larger than that expected naturally. The age-intensity of infection curve never satisfactorily took the form of those found in the field, and tended to mimic the age-exposure curves. Although one might call into question the assumption that the exposure data on females is representative of both sexes, it is felt that while allowance for an

age-dependent exposure factor goes some way in producing the familiar age-intensity of infection curve, still another factor is required. Lastly, it was interesting to note that no year's results displayed the breakpoint behaviour.

The value of models of transmission hopefully lies in the ability to predict the consequences of various control schemes. Despite imperfections noted above, it was of interest to study the behaviour of the model under changing values of parameters. Macdonald was an advocate of a joint chemotherapy and molluscicide intervention campaign and, as in the 1965 paper, this model was studied by varying the number of snails and lifespan of schistosomes. Regardless of which pairing situation was assumed, the 1967 results showed a decline in y^* as both factors were reduced. There was, however, no breakpoint below which eradication could be expected. When immigration and emigration of worms were omitted, the breakpoint phenomenon appeared, and the system behaved in a different fashion. The results obtained by changing the snail number for this model are identical to those when exposure within each age group is proportionally altered. This was noted by Macdonald and results from nearly identical assumptions relating these effects to the dynamics of transmission.

It was pointed out that the decision of which parameters (or variables) are altered when control measures are to be mimicked is not uniquely defined. The implications of chemotherapy control vary greatly if is assumed that the mean lifespan of schistosomes is reduced (possibly leading to breakpoint "washout" and no scope for reinfection) or the community mean wormload is reduced (possibly below a breakpoint, with

scope for reinfection). Snail control was studied by changing the fixed number of snails. If, however, the lifespan of infected snails is assumed decreased by molluscicide, one can expect different results. (These are not as dramatically different as in the chemotherapy case, but greater sensitivity to the parameter change is noted.)

2) Overall Impressions

While many look on a mathematical model as a basis for predictions, or an aid in deciding which control strategy is optimal (however defined), the "state of the art" for schistosomiasis is perhaps not sufficiently advanced to permit such uses. Bailey, (1975) on page 331 of his book, reminds us:

> It is clear that this work is still in the opening stages of development. An excellent start has been made, but much more needs to be done before models of the type evolved for malaria can be used in a practical way for schistosomiasis to facilitate the choice between alternative intervention strategies.

The potential usefulness of models at this stage lies in the detection of factors most relevant to transmission. To quote Macdonald (1965b, p.615)

> Even failure to produce a successful model may be a substantial aid because it demonstrates that one does not know, or does not appreciate the significance of, some factor which is indeed important.

What other factors might be considered to provide more satisfying results?

The consideration of the intermediate host to date seems to have facilitated mathematics at the expense of considerable reality. The survival of snails is assumed exponential and dynamics of the model are strongly influenced by parameters μ_2' and μ_2''. This assumption could be

fairly easily checked, yet there appears to be little evidence that this has been studied. More importantly, the number of snails is assumed constant and their distribution uniform. Barbour (1978) has shown interesting results when the latter assumption is relaxed. Sturrock et al (1974) have studied the effect of flowing and still habitats on the snail populations. This is reflected in the impressions held by epidemiologists that transmission possibly experiences seasonal variation, affected by varying rainfall. Prime consideration should be given to the developement of models less rigid in the treatment of snail populations.

The model considerations here go no way to resolve uniformity assumptions that affect the transmission parameters in the Macdonald-Nåsell-Hirsch formulation. The inaccuracy of the model predictions, based on poor parameter estimates obtained herein is possibly a consequence of this simplification. The methods of parameter estimation can readily be questioned but possibly more realistic results will be obtained from models admitting heterogeneity or non-uniformity. There needs to be a convergence in technique - the statistician needs to obtain better parameter estimates and the modeller needs to provide more realistic models simplifying parameter estimation.

Throughout, the three pairing situations, "together", "separate" and "Poisson", have been considered in parallel. There does not appear to be a strong basis for preference of any particular one. Frequently, the difference was of minor importance, and for analytic or computational work, the Poisson assumption could be used with little fear of invalid results and the other two reserved for improved results.

On the question of preference between using immunity or age-dependent exposure to "explain" the age by intensity of infection curve, there is no firm answer. Not unexpectedly, the age dependent exposure rates strongly determine the predicted intensities, and failure to obtain a convincing fit could be blamed on sampling errors of estimates of exposure parameters. It is more likely, however, that with the lack of sophistication in any like model formulation and parameter estimation, as well as sampling variation in observed age-egg load curves, it is infeasible to expect a sufficiently bad fit to disprove either hypothesis. When allowance is made for the diverseness of human behaviour, the confidence intervals about mean intensity of infections in humans will possibly be so large that most models will find observed results 'not significantly different' from predicted values. Quite possibly, different models will be devised and employed depending upon particular requirements without a firm belief that one factor (immunity or age dependent exposure) predominates. (A physical precedent for this is the use of wave and particle models in studying the behaviour of light.)

As the model described here is intended only as another step in the early stages of determining the most important factors influencing the transmission of schistosomiasis, a word of warning is warranted. No specific comments have been made concerning the control of transmission of infection in the Ravine Poisson area, and none are intended. The use of results (described particularly in Chapter Five) requires either belief in the assumptions made or robustness of the model to the assumptions. The former, throughout, has been criticized and no study of the latter has been attempted. The transmission of infection in Ravine Poisson has not been analysed here, rather the behaviour of a mathematical model has been studied.

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Table A-1

Human Population Movement in Area 1967 - 1977

For Year Y_i

A Born in Y_{i-1}, Y_i

B Immigrates in Y_{i-1}, Y_i

C Census Population

D Emigrates Y_i, Y_{i+1}

E Dies Y_i, Y_{i+1}

F Moves up to next age group Y_i, Y_{i+1}

G Population used in model. N_{1i}

1967

Age Group	A	B	C	D	E	F	G
0-4			47	4		14	46.5
5-9			44	1	1	6	49
10-14			27			4	28.5
15-19			27			6	26.5
20-29			13	1			15.5
30-39			17		1	2	16.5
40-49			27	1			28
50-59			13				13
60+			3				3

1969

0-4	11	6	46			12	46.5
5-9		4	54	2		16	53
10-14		1	30			7	34.5
15-19		1	26	2	1	5	25.5
20-29			18				22
30-39		2	16				16
40-49		1	29			1	28.5
50-59			13			1	13
60+			3				3.5

1970

0-4	8	5	47			7	49
5-9		4	52	2		6	55.5
10-14			39	1		5	43
15-19			25			5	28
20-29		3	26	1		3	30
30-39			16			2	17.5
40-49			28				30
50-59			13			1	12.5
60+			4				5.5

Table A-1 (cont.)

1971

Age Group	A	B	C	D	E	F	G
0-4	5	6	51			20	46
5-9		8	59			7	67.5
10-14		8	47			10	47
15-19		6	31			7	32.5
20-29		7	34	1		1	38
30-39		2	19			3	18.5
40-49		2	32			7	30
50-59			12			2	14.5
60+		2	7				8

1972

0-4	9	1	41	2		11	40
5-9		4	76	7		16	72.5
10-14		3	47	5		4	51.5
15-19			34	7		4	33
20-29		3	42	9		1	42
30-39		1	18	1		2	18
40-49			28	1		6	28
50-59			17			1	21.5
60+			9	1			12

1973

0-4	5	6	39	4		8	37.5
5-9		5	69	3		10	69
10-14		2	56	3		11	54.5
15-19		5	32	2		5	35
20-29		6	42	7		3	40.5
30-39		2	18			4	18.5
40-49		5	28	1		3	28.5
50-59		4	26	?		2	26
60+		6	15		1		15.5

1974

0-4	3	6	36	2		8	45
5-9		5	69	6		13	74
10-14		1	53	2	1	12	58
15-19		2	38	2		5	45.5
20-29		2	39	8		6	45
30-39		2	19			1	24.5
40-49		1	29	4		2	28.5
50-59		1	26	2		3	27
60+			16	1	1		19.5

Table A-1 (cont.)

1975

Age Group	A	B	C	D	E	F	G
0-4	11	17	54	4		15	50
5-9		21	79	7		17	77
10-14		12	63	4		10	67.5
15-19		10	53	6		10	51
20-29		21	51	13		6	51
30-39		6	30	1		2	33.5
40-49		4	28	1		2	29.5
50-59		5	28	1		1	29.5
60+		6	23	1	1		22.5

1976

0-4	3	8	46	3		4	53.5
5-9		5	75	7	1	16	69
10-14		6	72	9		8	73
15-19		2	49	12		5	47
20-29		9	51	12		2	52.5
30-39		4	37	4			37.5
40-49		4	31	4		5	26.5
50-59		3	31	3		3	31
60+			22		1		23.5

1977

0-4	14	8	61
5-9		7	63
10-14		4	74
15-19		5	45
20-29		12	54
30-39		3	38
40-49			22
50-59		1	31
60+		1	25

Table A-2

Observed and Fitted Distributions of Worm Pairs for Together, Separate and Poisson Situation.

1967	Worm Pairs	Observed	Together	Separate	Poisson
	0-39	184	181	176	211
	40-79	6	13	13	8
	80-119	11	7	6	0
	120-159	2	5	4	0
	160-199	7	3	2	0
	200-239	2	2	2	0
	240-279	2	2	1	0
	280+	4	6	15	0
		218			
1969	0-9	141	123	126	0
	10-19	36	38	38	118
	20-29	0	23	22	115
	30-39	27	15	14	1
	40+	31	37	37	0
		235			
1970	0-9	145	149	150	14
	10-19	43	39	39	220
	20-29	3	22	21	17
	30-39	0	14	13	0
	40-49	58	9	9	0
	50+	1	18	19	0
		250			
1971	0-19	226	237	237	288
	20-39	30	25	24	4
	40-59	28	12	11	0
	60-79	1	7	5	0
	80-99	0	4	4	0
	100-119	5	3	3	0
	120+	2	4	9	0
		292			

Table A-2 (cont.)

1972	Worm Pairs	Observed	Together	Separate	Poisson
	0-19	270	254	254	311
	20-39	5	39	38	1
	40-59	35	12	12	0
	60+	2	7	8	0
		312			
1973	0-19	277	276	276	325
	20-39	36	26	24	0
	40-59	6	11	10	0
	60-79	3	5	5	0
	80+	3	6	10	0
		325			
1974	0-7	172	219	220	86
	8-15	65	43	43	236
	16-23	44	23	22	3
	24-31	40	14	13	0
	32+	4	26	27	0
		325			
1975	0-9	338	354	345	368
	10-19	29	18	19	41
	20-29	4	10	9	0
	30-39	17	6	5	0
	40-49	9	4	3	0
	50-59	3	3	2	0
	60-69	4	2	2	0
	70+	5	11	23	0
		409			
1976	0-3	382	381	380	407
	4-7	4	27	11	7
	8-11	11	5	5	0
	12-15	0	1	3	0
	16-19	11	0	2	0
	20+	6	0	14	0
		414			

Table A-2 (cont.)

1977	Worm Pairs	Observed	Together	Separate	Poisson
	0-3	403	401	398	413
	4-7	7	5	5	0
	8-11	0	2	2	0
	12-15	0	1	1	0
	16+	3	3	8	0
		413			

Table A-3

Values of Input Parameters and Initial Values for Years 1967 to 1969

$\lambda_1 = 162.5$ $\lambda_2 = 336$ $p_2 = .248 \times 10^{-7}$ $\tau = 35$ $N_2 = 76500$ $k = .128$ (together)
$\mu_1 = 0.001$ $\mu_2' = .00834$ $\mu_2'' = .00834$ $y(t=0) = .005$ $k = .209$ (separate)

i	Age Group	$N_{\cdot i}$	p_{1_i}	δ_i/N_{1_i}	η_i/N_{1_i}	ξ_i/N_{1_i}
1	0-4	46.5	$.349 \times 10^{-10}$	$.157 \times 10^{-3}$	$.549 \times 10^{-3}$	$.521 \times 10^{-3}$
2	5-9	49.0	$.324 \times 10^{-9}$	$.745 \times 10^{-4}$	$.223 \times 10^{-3}$	$.384 \times 10^{-3}$
3	10-14	28.5	$.130 \times 10^{-8}$	0	$.256 \times 10^{-3}$	$.275 \times 10^{-3}$
4	15-19	26.5	$.259 \times 10^{-8}$	0	$.413 \times 10^{-3}$	$.706 \times 10^{-3}$
5	20-29	15.5	$.236 \times 10^{-8}$	$.118 \times 10^{-3}$	0	0
6	30-39	16.5	$.648 \times 10^{-8}$	$.111 \times 10^{-3}$	$.221 \times 10^{-3}$	$.130 \times 10^{-3}$
7	40-49	28.0	$.164 \times 10^{-8}$	$.652 \times 10^{-4}$	0	0
8	50-59	13.0	$.308 \times 10^{-8}$	0	0	0
9	60+	3.0	$.629 \times 10^{-8}$	0	-	0

		$m_i(t=0)$			ε_i/N_{1_i}		
i	Age Group	Together	Separate	Poisson	Together	Separate	Poisson
1	0-4	2.0	8.4	2.2	$.135 \times 10^{-2}$	$.280 \times 10^{-2}$	$.147 \times 10^{-2}$
2	5-9	28.0	124.4	30.2	$.147 \times 10^{-2}$	$.321 \times 10^{-2}$	$.159 \times 10^{-2}$
3	10-14	311.4	1448.0	319.2	$.118 \times 10^{-1}$	$.299 \times 10^{-1}$	$.120 \times 10^{-1}$
4	15-19	94.2	432.6	97.6	$.493 \times 10^{-2}$	$.120 \times 10^{-1}$	$.507 \times 10^{-2}$
5	20-29	30.8	137.0	33.0	0	0	0
6	30-39	65.0	296.4	67.8	$.876 \times 10^{-2}$	$.208 \times 10^{-1}$	$.911 \times 10^{-2}$
7	40-49	7.8	32.8	8.8	$.704 \times 10^{-3}$	$.151 \times 10^{-2}$	$.769 \times 10^{-3}$
8	50-59	5.6	23.8	6.4	0	0	0
9	60+	0.0	0.0	0.0	0	0	0

Table A-3 (cont.)

Values of Input Parameters and Initial Values for Variables for Year 1969-1970

$\lambda_1 = 162.5$ $\lambda_2 = 336$ $p_2 = .248 \times 10^{-7}$ $\tau = 35$ $N_2 = 52500$ $k = .529$ (together)

$\mu_1 = .001$ $\mu_2' = .00834$ $\mu_2'' = .00834$ $y(t=0) = .0025$ $k = .531$ (separate)

i	Age Group	N_{1_i}	p_{1_i}	δ_i/N_{1_i}	η_i/N_{1_i}	ξ_i/N_{1_i}
1	0-4	46.5	$.349 \times 10^{-10}$	0	$.707 \times 10^{-3}$	-
2	5-9	53.0	$.559 \times 10^{-10}$	$.103 \times 10^{-3}$	$.827 \times 10^{-3}$	$.620 \times 10^{-3}$
3	10-14	34.5	$.224 \times 10^{-9}$	0	$.556 \times 10^{-3}$	$.127 \times 10^{-2}$
4	15-19	25.5	$.447 \times 10^{-9}$	$.322 \times 10^{-3}$	$.537 \times 10^{-3}$	$.752 \times 10^{-3}$
5	20-29	22.0	$.406 \times 10^{-9}$	0	0	$.623 \times 10^{-3}$
6	30-39	16.0	$.112 \times 10^{-8}$	0	0	0
7	40-49	28.5	$.283 \times 10^{-9}$	0	$.961 \times 10^{-4}$	0
8	50-59	13.0	$.531 \times 10^{-9}$	0	$.211 \times 10^{-3}$	$.211 \times 10^{-3}$
9	60+	3.5	$.109 \times 10^{-8}$	0	-	$.783 \times 10^{-3}$

i	Age Group	$m_i(t=0)$ Together	$m_i(t=0)$ Separate	$m_i(t=0)$ Poisson	ϵ_i/N_{1_i} Together	ϵ_i/N_{1_i} Separate	ϵ_i/N_{1_i} Poisson
1	0-4	8.8	20.2	9.2	0	0	0
2	5-9	10.6	23.4	11.4	$.445 \times 10^{-3}$	$.920 \times 10^{-3}$	$.486 \times 10^{-3}$
3	10-14	192.2	487.4	195.4	0	0	0
4	15-19	71.6	173.6	73.6	0	0	0
5	20-29	28.8	66.8	30.2	$.104 \times 10^{-1}$	$.249 \times 10^{-1}$	$.108 \times 10^{-1}$
6	30-39	39.6	94.0	41.2	0	0	0
7	40-49	10.8	23.4	11.8	0	0	0
8	50-59	10.8	23.4	11.8	0	0	0
9	60+	0	0	0	0	0	0

Table A-3 (cont.)

Values of Input Parameters and Initial Values for Variables for Year 1970-1971

$\lambda_1 = 162.5$ $\lambda_2 = 336$ $p_2 = .248 \times 10^{-7}$ $\tau = 35$ $N_2 = 0$ $k = .5065$ (together)

$\mu_1 = .001$ $\mu_2' = .00834$ $\mu_2'' = .00834$ $k = .5100$ (separate)

i	Age Group	N_{1_i}	p_{1_i}	δ_i/N_{1_i}	η_i/N_{1_i}	ξ_i/N_{1_i}
1	0-4	49.0	$.374 \times 10^{-10}$	0	$.391 \times 10^{-3}$	0
2	5-9	55.5	$.602 \times 10^{-10}$	$.987 \times 10^{-4}$	$.296 \times 10^{-3}$	$.346 \times 10^{-3}$
3	10-14	43.0	$.203 \times 10^{-9}$	$.596 \times 10^{-4}$	$.319 \times 10^{-3}$	$.382 \times 10^{-3}$
4	15-19	28.0	$.459 \times 10^{-9}$	0	$.489 \times 10^{-3}$	$.489 \times 10^{-3}$
5	20-29	30.0	$.336 \times 10^{-9}$	$.913 \times 10^{-4}$	$.274 \times 10^{-3}$	$.457 \times 10^{-3}$
6	30-39	17.5	$.115 \times 10^{-8}$	0	$.313 \times 10^{-3}$	$.470 \times 10^{-3}$
7	40-49	30.0	$.303 \times 10^{-9}$	0	0	$.183 \times 10^{-3}$
8	50-59	12.5	$.623 \times 10^{-9}$	0	$.219 \times 10^{-3}$	0
9	60+	5.5	$.782 \times 10^{-9}$	0	-	$.498 \times 10^{-3}$

i	Age Group	$m_i(t=0)$ Together	$m_i(t=0)$ Separate	$m_i(t=0)$ Poisson	ε_i/N_{1_i} Together	ε_i/N_{1_i} Separate	ε_i/N_{1_i} Poisson
1	0-4	3.6	8.0	4.0	0	0	0
2	5-9	7.2	15.8	7.6	0	0	0
3	10-14	82.4	204.0	84.6	$.159 \times 10^{-1}$	$.553 \times 10^{-1}$	$.166 \times 10^{-1}$
4	15-19	101.0	250.6	103.4	$.268 \times 10^{-1}$	$.953 \times 10^{-1}$	$.277 \times 10^{-1}$
5	20-29	40.2	96.0	41.8	$.256 \times 10^{-1}$	$.879 \times 10^{-1}$	$.269 \times 10^{-1}$
6	30-39	33.0	78.0	34.6	$.126 \times 10^{-1}$	$.437 \times 10^{-1}$	$.132 \times 10^{-1}$
7	40-49	10.8	23.4	11.8	$.175 \times 10^{-2}$	$.566 \times 10^{-2}$	$.194 \times 10^{-2}$
8	50-59	10.8	23.4	11.8	0	0	0
9	60+	0	0	0	0	0	0

Table A-3 (cont.)

Values of Input Parameters and Initial Values for Variables for Year 1971-1972

$\lambda_1 = 162.5$ $\lambda_2 = 336$ $p_2 = .248 \times 10^{-7}$ $\tau = 35$ $N_2 = 0$ $k = .242$ (together)
$\mu_1 = .001$ $\mu_2' = .00834$ $\mu_2'' = .00834$ $k = .295$ (separate)

i	Age Group	N_{1_i}	p_{1_i}	δ_i/N_{1_i}	η_i/N_{1_i}	ξ_i/N_{1_i}
1	0-4	46.0	$.675 \times 10^{-10}$	0	$.119 \times 10^{-3}$	-
2	5-9	67.5	$.839 \times 10^{-10}$	0	$.284 \times 10^{-3}$	$.812 \times 10^{-3}$
3	10-14	47.0	$.314 \times 10^{-9}$	0	$.583 \times 10^{-3}$	$.408 \times 10^{-3}$
4	15-19	32.5	$.670 \times 10^{-9}$	0	$.590 \times 10^{-3}$	$.843 \times 10^{-3}$
5	20-29	38.0	$.450 \times 10^{-9}$	$.721 \times 10^{-4}$	$.721 \times 10^{-4}$	$.505 \times 10^{-3}$
6	30-39	18.5	$.185 \times 10^{-8}$	0	$.444 \times 10^{-3}$	$.148 \times 10^{-3}$
7	40-49	30.0	$.513 \times 10^{-9}$	0	$.639 \times 10^{-3}$	$.274 \times 10^{-3}$
8	50-59	14.5	$.910 \times 10^{-9}$	0	$.378 \times 10^{-3}$	$.132 \times 10^{-3}$
9	60+	8.0	$.911 \times 10^{-9}$	0	-	$.685 \times 10^{-3}$

i	Age Group	$m_i(t=0)$ Together	$m_i(t=0)$ Separate	$m_i(t=0)$ Poisson	ε_i/N_{1_i} Together	ε_i/N_{1_i} Separate	ε_i/N_{1_i} Poisson
1	0-4	.6	2.0	.6	$.119 \times 10^{-2}$	$.258 \times 10^{-2}$	$.126 \times 10^{-2}$
2	5-9	19.6	68.8	20.4	$.349 \times 10^{-3}$	$.698 \times 10^{-3}$	$.382 \times 10^{-3}$
3	10-14	45.4	155.6	47.8	$.303 \times 10^{-1}$	$.749 \times 10^{-1}$	$.307 \times 10^{-1}$
4	15-19	94.4	333.0	97.8	0	0	0
5	20-29	32.8	111.8	34.8	$.812 \times 10^{-2}$	$.184 \times 10^{-1}$	$.844 \times 10^{-2}$
6	30-39	21.0	69.8	22.6	$.228 \times 10^{-2}$	$.489 \times 10^{-2}$	$.246 \times 10^{-2}$
7	40-49	10.2	32.8	11.4	0	0	0
8	50-59	12.0	38.2	11.4	0	0	0
9	60+	0.0	0	0	0	0	0

Table A-3 (cont.)

Values of Input Parameters and Initial Values for Variables for Year 1972-1973

$\lambda_1 = 162.5$ $\lambda_2 = 336$ $p_2 = .248 \times 10^{-7}$ $\tau = 35$ $N_2 = 0$ $k = .551$ (together)

$\mu_i = .001$ $\mu_2' = .00834$ $\mu_2'' = .00834$ $k = .553$ (separate)

i	Age Group	N_{1_i}	p_{1_i}	δ_i/N_{1_i}	η_i/N_{1_i}	ξ_i/N_{1_i}
1	0-4	40.0	$.675 \times 10^{-10}$	$.137 \times 10^{-3}$	$.753 \times 10^{-3}$	-
2	5-9	72.5	$.839 \times 10^{-10}$	$.265 \times 10^{-3}$	$.605 \times 10^{-3}$	$.416 \times 10^{-3}$
3	10-14	51.5	$.314 \times 10^{-9}$	$.266 \times 10^{-3}$	$.218 \times 10^{-3}$	$.851 \times 10^{-3}$
4	15-19	33.0	$.670 \times 10^{-9}$	$.581 \times 10^{-3}$	$.332 \times 10^{-3}$	$.332 \times 10^{-3}$
5	20-29	42.0	$.450 \times 10^{-9}$	$.587 \times 10^{-3}$	$.652 \times 10^{-3}$	$.261 \times 10^{-3}$
6	30-39	18.0	$.185 \times 10^{-8}$	$.152 \times 10^{-3}$	$.304 \times 10^{-3}$	$.152 \times 10^{-3}$
7	40-49	28.0	$.513 \times 10^{-9}$	$.979 \times 10^{-4}$	$.587 \times 10^{-3}$	$.196 \times 10^{-3}$
8	50-59	21.5	$.910 \times 10^{-9}$	0	$.127 \times 10^{-3}$	$.765 \times 10^{-3}$
9	60+	12.0	$.911 \times 10^{-9}$	$.228 \times 10^{-3}$	-	$.228 \times 10^{-3}$

i	Age Group	$m_i(t=0)$ Together	$m_i(t=0)$ Separate	$m_i(t=0)$ Poisson	ε_i/N_{1_i} Together	ε_i/N_{1_i} Separate	ε_i/N_{1_i} Poisson
1	0-4	1.0	2.2	1.0	0	0	0
2	5-9	8.4	18.2	9.0	$.280 \times 10^{-2}$	$.910 \times 10^{-2}$	$.302 \times 10^{-2}$
3	10-14	30.6	70.8	31.6	$.296 \times 10^{-2}$	$.958 \times 10^{-2}$	$.319 \times 10^{-2}$
4	15-19	92.8	219.4	95.0	$.821 \times 10^{-1}$	.294	$.838 \times 10^{-1}$
5	20-29	37.6	85.2	39.0	$.418 \times 10^{-1}$	.146	$.432 \times 10^{-1}$
6	30-39	15.4	33.0	16.6	0	0	0
7	40-49	17.8	38.2	18.8	$.787 \times 10^{-2}$	$.258 \times 10^{-1}$	$.845 \times 10^{-2}$
8	50-59	14.6	31.0	15.6	$.116 \times 10^{-1}$	$.390 \times 10^{-1}$	$.123 \times 10^{-1}$
9	60+	6.2	12.0	6.8	$.485 \times 10^{-2}$	.165	$.509 \times 10^{-1}$

Table A-3 (cont.)

Values of Input Parameters and Initial Values for Variables for Year 1973-1974

$\lambda_1 = 162.5$ $\lambda_2 = 336$ $p_2 = .248 \times 10^{-7}$ $\tau = 35$ $N_2 = 0$ $k = .247$ (together)

$\mu_1 = .001$ $\mu_2' = .00834$ $\mu_2'' = .00834$ $k = .301$ (separate)

i	Age Group	N_{1_i}	p_{1_i}	δ_i/N_{1_i}	η_i/N_{1_i}	ξ_i/N_{1_i}
1	0-4	37.5	$.675 \times 10^{-10}$	$.219 \times 10^{-3}$	$.822 \times 10^{-3}$	-
2	5-9	69.0	$.839 \times 10^{-10}$	$.249 \times 10^{-3}$	$.605 \times 10^{-3}$	$.534 \times 10^{-3}$
3	10-14	54.5	$.314 \times 10^{-9}$	$.162 \times 10^{-3}$	$.406 \times 10^{-3}$	$.690 \times 10^{-3}$
4	15-19	35.0	$.670 \times 10^{-9}$	$.322 \times 10^{-3}$	$.537 \times 10^{-3}$	$.537 \times 10^{-3}$
5	20-29	40.5	$.450 \times 10^{-9}$	$.698 \times 10^{-3}$	$.322 \times 10^{-3}$	$.537 \times 10^{-3}$
6	30-39	18.5	$.185 \times 10^{-8}$	$.818 \times 10^{-4}$	$.164 \times 10^{-3}$	$.491 \times 10^{-3}$
7	40-49	28.5	$.513 \times 10^{-9}$	$.929 \times 10^{-4}$	$.186 \times 10^{-3}$	$.186 \times 10^{-3}$
8	50-59	26.0	$.910 \times 10^{-9}$	$.929 \times 10^{-4}$	$.929 \times 10^{-4}$	$.186 \times 10^{-3}$
9	60+	15.5	$.911 \times 10^{-9}$	$.249 \times 10^{-3}$	-	$.122 \times 10^{-3}$

		$m_i(t=0)$			ϵ_i/N_{1_i}		
i	Age Group	Together	Separate	Poisson	Together	Separate	Poisson
1	0-4	.4	1.6	.6	0	0	0
2	5-9	7.0	23.2	7.6	0	0	0
3	10-14	17.0	55.6	18.4	0	0	0
4	15-19	68.4	236.4	71.0	$.997 \times 10^{-2}$	$.269 \times 10^{-1}$	$.103 \times 10^{-1}$
5	20-29	36.8	123.4	39.0	$.589 \times 10^{-2}$	$.155 \times 10^{-1}$	$.617 \times 10^{-2}$
6	30-39	14.0	46.2	15.2	$.714 \times 10^{-3}$	$.184 \times 10^{-2}$	$.761 \times 10^{-3}$
7	40-49	19.6	65.6	20.8	$.807 \times 10^{-2}$	$.188 \times 10^{-2}$	$.904 \times 10^{-2}$
8	50-59	20.2	66.0	21.6	$.207 \times 10^{-2}$	$.527 \times 10^{-2}$	$.223 \times 10^{-2}$
9	60+	24.0	80.2	25.6	0	0	0

Table A-3 (cont.)

Values of Input Parameters and Initial Values for Variables for Year 1974-1975

$\lambda_1 = 162.5$ $\lambda_2 = 336$ $p_2 = .248 \times 10^{-7}$ $\tau = 35$ $N_2 = 0$ $k = .388$ (together)

$\mu_1 = .001$ $\mu_2' = .00834$ $\mu_2'' = .00834$ $k = .424$ (separate)

i	Age Group	N_{1_i}	p_{1_i}	δ_i/N_{1_i}	η_i/N_{1_i}	ξ_i/N_{1_i}
1	0-4	45.0	$.675 \times 10^{-10}$	$.122 \times 10^{-3}$	$.487 \times 10^{-3}$	-
2	5-9	74.0	$.839 \times 10^{-10}$	$.222 \times 10^{-3}$	$.481 \times 10^{-3}$	$.296 \times 10^{-3}$
3	10-14	58.0	$.314 \times 10^{-9}$	$.142 \times 10^{-3}$	$.567 \times 10^{-3}$	$.614 \times 10^{-3}$
4	15-19	45.5	$.670 \times 10^{-9}$	$.120 \times 10^{-3}$	$.301 \times 10^{-3}$	$.723 \times 10^{-3}$
5	20-29	45.0	$.450 \times 10^{-9}$	$.487 \times 10^{-3}$	$.365 \times 10^{-3}$	$.304 \times 10^{-3}$
6	30-39	24.5	$.185 \times 10^{-8}$	0	$.112 \times 10^{-3}$	$.671 \times 10^{-3}$
7	40-49	28.5	$.513 \times 10^{-9}$	$.385 \times 10^{-3}$	$.192 \times 10^{-3}$	$.961 \times 10^{-4}$
8	50-59	27.0	$.910 \times 10^{-9}$	$.203 \times 10^{-3}$	$.304 \times 10^{-3}$	$.203 \times 10^{-3}$
9	60+	19.5	$.911 \times 10^{-9}$	$.281 \times 10^{-3}$	-	$.422 \times 10^{-3}$

i	Age Group	$m_i(t=0)$ Together	$m_i(t=0)$ Separate	$m_i(t=0)$ Poisson	ε_i/N_{1_i} Together	ε_i/N_{1_i} Separate	ε_i/N_{1_i} Poisson
1	0-4	0	0	0	0	0	0
2	5-9	1.2	3.0	1.2	$.674 \times 10^{-3}$	$.341 \times 10^{-2}$	$.785 \times 10^{-3}$
3	10-14	24.6	66.6	25.6	0	0	0
4	15-19	58.6	157.8	61.0	$.211 \times 10^{-2}$	$.109 \times 10^{-1}$	$.235 \times 10^{-2}$
5	20-29	43.6	114.8	45.6	$.261 \times 10^{-1}$	.138	$.282 \times 10^{-1}$
6	30-39	24.0	62.0	25.6	$.358 \times 10^{-2}$	$.180 \times 10^{-1}$	$.420 \times 10^{-2}$
7	40-49	7.6	17.6	8.4	$.111 \times 10^{-1}$	$.590 \times 10^{-1}$	$.120 \times 10^{-1}$
8	50-59	22.4	58.0	23.8	$.218 \times 10^{-1}$	.116	$.233 \times 10^{-1}$
9	60+	17.4	43.8	18.8	$.116 \times 10^{-1}$	$.583 \times 10^{-1}$	$.135 \times 10^{-1}$

Table A-3 (cont.)

Values of Input Parameters and Initial Values for Variables for Year 1975-1976

$\lambda_1 = 162.5$ $\lambda_2 = 336$ $p_2 = .248 \times 10^{-7}$ $\tau = 35$ $N_2 = 0$ $k = .090$ (together)

$\mu_1 = .001$ $\mu_2' = .00834$ $\mu_2'' = .00834$ $k = .167$ (separate)

i	Age Group	$N1_i$	$p1_i$	$\delta_i/N1_i$	$\eta_i/N1_i$	$\xi_i/N1_i$
1	0-4	50.0	$.675 \times 10^{-10}$	$.219 \times 10^{-3}$	$.822 \times 10^{-3}$	-
2	5-9	77.0	$.839 \times 10^{-10}$	$.249 \times 10^{-3}$	$.605 \times 10^{-3}$	$.534 \times 10^{-3}$
3	10-14	67.5	$.314 \times 10^{-9}$	$.162 \times 10^{-3}$	$.406 \times 10^{-3}$	$.690 \times 10^{-3}$
4	15-19	51.0	$.670 \times 10^{-9}$	$.322 \times 10^{-3}$	$.537 \times 10^{-3}$	$.537 \times 10^{-3}$
5	20-29	51.0	$.450 \times 10^{-9}$	$.698 \times 10^{-3}$	$.322 \times 10^{-3}$	$.537 \times 10^{-3}$
6	30-39	33.5	$.185 \times 10^{-8}$	$.818 \times 10^{-4}$	$.164 \times 10^{-3}$	$.491 \times 10^{-3}$
7	40-49	29.5	$.513 \times 10^{-9}$	$.928 \times 10^{-4}$	$.186 \times 10^{-3}$	$.186 \times 10^{-3}$
8	50-59	29.5	$.910 \times 10^{-9}$	$.928 \times 10^{-4}$	$.929 \times 10^{-4}$	$.186 \times 10^{-3}$
9	60+	22.5	$.911 \times 10^{-9}$	$.249 \times 10^{-3}$	-	$.122 \times 10^{-3}$

i	Age Group	$m_i(t=0)$ Together	$m_i(t=0)$ Separate	$m_i(t=0)$ Poisson	$\epsilon_i/N1_i$ Together	$\epsilon_i/N1_i$ Separate	$\epsilon_i/N1_i$ Poisson
1	0-4	.6	3.4	.8	0	0	0
2	5-9	.2	1.2	.2	$.174 \times 10^{-2}$	$.119 \times 10^{-1}$	$.193 \times 10^{-2}$
3	10-14	19.6	105.4	21.0	$.140 \times 10^{-2}$	$.942 \times 10^{-2}$	$.158 \times 10^{-2}$
4	15-19	26.4	140.2	28.6	0	0	0
5	20-29	27.2	142.8	29.8	$.965 \times 10^{-2}$	$.662 \times 10^{-1}$	$.106 \times 10^{-1}$
6	30-39	16.8	89.4	18.4	0	0	0
7	40-49	4.8	25.2	5.2	$.854 \times 10^{-3}$	$.550 \times 10^{-2}$	$.110 \times 10^{-2}$
8	50-59	27.4	147.2	29.4	0	0	0
9	60+	14.6	76.2	16.2	0	0	0

Table A-3 (cont.)

Values of Input Parameters and Initial Values for Variables for Year 1976-1977

$\lambda_1 = 162.5$ $\lambda_2 = 336$ $p_2 = .248 \times 10^{-7}$ $\tau = 35$ $N_2 = 0$ $k = .052$ (together)

$\mu_1 = .001$ $\mu_2' = .00834$ $\mu_2'' = .00834$ $k = .122$ (separate)

i	Age Group	$N1_i$	$p1_i$	$\delta_i/N1_i$	$\eta_i/N1_i$	$\varepsilon_i/N1_i$
1	0-4	53.5	$.675 \times 10^{-10}$	$.154 \times 10^{-3}$	$.205 \times 10^{-3}$	-
2	5-9	69.0	$.839 \times 10^{-10}$	$.318 \times 10^{-3}$	$.635 \times 10^{-3}$	$.159 \times 10^{-3}$
3	10-14	73.0	$.314 \times 10^{-9}$	$.338 \times 10^{-3}$	$.300 \times 10^{-3}$	$.601 \times 10^{-3}$
4	15-19	47.0	$.670 \times 10^{-9}$	$.700 \times 10^{-3}$	$.292 \times 10^{-3}$	$.466 \times 10^{-3}$
5	20-29	52.5	$.450 \times 10^{-9}$	$.626 \times 10^{-3}$	$.104 \times 10^{-3}$	$.261 \times 10^{-3}$
6	30-39	37.5	$.185 \times 10^{-8}$	$.292 \times 10^{-3}$	0	$.146 \times 10^{-3}$
7	40-49	26.5	$.513 \times 10^{-9}$	$.414 \times 10^{-3}$	$.517 \times 10^{-3}$	0
8	50-59	31.0	$.910 \times 10^{-9}$	$.265 \times 10^{-3}$	$.265 \times 10^{-3}$	$.442 \times 10^{-3}$
9	60+	23.5	$.911 \times 10^{-9}$	$.117 \times 10^{-3}$	-	$.350 \times 10^{-3}$

i	Age Group	$m_i(t=0)$ Together	$m_i(t=0)$ Separate	$m_i(t=0)$ Poisson	$\varepsilon_i/N1_i$ Together	$\varepsilon_i/N1_i$ Separate	$\varepsilon_i/N1_i$ Poisson
1	0-4	0	0	0	0	0	0
2	5-9	1.4	9.0	1.6	0	0	0
3	10-14	2.4	16.2	2.8	0	0	0
4	15-19	3.4	22.8	4.2	0	0	0
5	20-29	10.2	68.4	11.6	$.837 \times 10^{-2}$	$.747 \times 10^{-1}$	$.933 \times 10^{-2}$
6	30-39	.4	2.4	.4	0	0	0
7	40-49	1.4	9.4	1.8	0	0	0
8	50-59	0	0	0	0	0	0
9	60+	2.4	16.6	3.0	0	0	0

Glossary

1) ROMAN SYMBOLS

Symbol	Main Reference	Units where Applicable
A	11	schistosomes per snail
B	10	snails per day
E	7	entries per day
e	8	ova per schistosome lifetime
h	11,48	snails per day
k	70	-
k_1	8	-
k_2	11	-
L	7	metres
m	7	schistosomes per human
m_j	42	schistosomes per human
N_1	24	humans
N_2	43	snails
N_{1_i}	42	humans
n	10	days
P	7	humans
p	22	per day
P_1	23	schistosomes per cercaria
P_2	23,43	snails per miracidium
P_{1_i}	44	schistosomes per cercaria
r	8	per day
S	7	snails
T_1	24	-
T_2	24	-
W	52	paired schistosomes
x	42	uninfected snails
y	24,42	patent snails
z	42	prepatent snails
z_1	8	miracidia per schistosome
z_2	10	miracidia per schistosome

2) GREEK SYMBOLS

Symbols	Main Reference	Units
α	7	paired schistosomes per schistosome
δ_i	45	humans per day
ε_i	46	schistosomes per day
η_i	45	humans per day
λ_1	23,43	miracidia per paired schistosome per day
λ_2	23,43	cercariae per snail per day
μ_1	22,44	per day
μ_2'	44	per day
μ_2''	44	per day
μ_2	22,44	per day
ν_1	23	schistosomes per snail
ν_2	23	snails per paired schistosome
ξ_i	45	humans per day
Π_s	71	-
Π_t	71	-
τ	44	days
ϕ_s	71	paired schistosomes per schistosome
ϕ_t	71	paired schistosomes per schistosome

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On Allowing for Diagnostic Imperfections in Assessing Effectiveness of Treatment for *Schistosomiasis*

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Some possible effects of misdiagnosis for *Schistosomiasis* in epidemiological measurements are investigated. With greater chances of misdiagnosis for lower prevalence levels, expectations of control programmes might be reassessed. As prevalence decreases, the fraction of missed positives over all apparent negatives need not uniformly decrease. In control situations even perfect treatment rates may produce very small changes in prevalence and other indices of infectivity level.

INTRODUCTION

Knowledge of the transmission of the disease *Schistosomiasis* has benefited from the large-scale experiments undertaken to establish effective means of control. The design and aims of these studies can frequently be seen as similar to those of their smaller counterparts, clinical trials. Whereas the latter may deal with as many factors or treatments at various levels in different combinations as the former, the size and lesser degree of control of the former can be expected to introduce further complications.

In routine survey work for *Schistosomiasis* there needs to be a substantial laboratory to process samples for deriving even the simplest measure of infection in a population, that of prevalence. With a large system geared to processing big numbers there is an expected price to pay in terms of accuracy. Indeed, as prevalence (and other indices) drop in the St Lucia project, diagnostic imperfection may play an important role and this should be borne in mind while scrutinizing results or setting goals. This paper is a first attempt to explore one possible quantification of the matter.

SENSITIVITY, FALSE POSITIVES AND FALSE NEGATIVES

In any test for an infection there are chances of mistaken diagnoses. One might incorrectly assess a truly infected case to be not positive, or equally one might incorrectly claim a truly uninfected individual to be positive. The rates at which true cases are deemed positive, and true infection-free individuals are diagnosed negative are called the 'sensitivity' and 'specificity' respectively of the test. Two measures of practical importance are the proportions of misdiagnoses of the apparent positives and negatives (and not the true positives and negatives). These proportions depend not only upon the sensitivity and specificity of the performance of any test, but also upon the prevalence of the infection in the population studied. In particular, for a fixed sensitivity and specificity, as the prevalence of infection in a population decreases to zero, the proportion of false positives of those apparently positive rises to one, while the proportion of false negatives of those apparently negative decreases to zero (1).

A standard layout for such data is presented in Table I with prevalence indicated by p, specificity by $1-\alpha$ and sensitivity by $1-\beta$.

In the diagnosis of infection of *Schistosomiasis* both types of error are likely. It is not unreasonable to assume the chances of misdiagnosing an uninfected person are minimal: foreign material in stool samples are not likely to be confused with eggs. There is another source of declaring an individual falsely positive, the detection of residual eggs in faeces following successful treatment (or spontaneous death of the last schistosome) of a patient. Provided care is taken in studying recently treated patients, it seems likely that the specificity of the diagnostic technique should remain rea-

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TABLE I

Distribution of individuals according to presence of disease and results of diagnosis

	Diagnosis		
	Positive	Negative	Total
Disease status			
Truly Infected	$p(1-\beta)$	$p\beta$	p
Truly not infected	$(1-p)\alpha$	$(1-p)(1-\alpha)$	$(1-p)$

sonably constant and independent of the prevalence. Grave doubts, however, would be expressed to assuming sensitivity independent of prevalence.

The relationship between prevalence and intensity of infection as determined by the number of excreted eggs in stools has received both empirical and theoretical investigations. Jordan (4) mentions data from Brazil, Tanzania and St Lucia which affirm that populations with higher prevalence have associated higher intensity of infection. May (5) and Bradley and May (2) provide theoretical relationships under assumptions of worm aggregation in hosts.

Thus, consider relaxing the assumption of constant sensitivity and allow it to be related to prevalence. At higher prevalence, one anticipates greater intensity of infection and less chance of missed positives. As prevalence decreases, allow intensity to decrease and the chance of missed positives to increase. Figure 1 suggests the shape of such curves.

The proportion of false positives of those apparently positive involves an application of Bayes theorem and is algebraically:

$$\psi = \frac{(1-p)\,\alpha}{(1-p)\,\alpha + p\,(1-\beta)} = \frac{1}{1+\dfrac{g}{(1-p)\,\alpha}} \quad (1)$$

where $g = p\,(1-\beta)$.

The proportion of false negatives of those apparently negative is:

$$\varphi = \frac{p\beta}{p\beta + (1-p)\,(1-\alpha)} = \frac{1}{1+\dfrac{(1-p)\,(1-\alpha)}{f}} \quad (2)$$

where $f = p\beta$.

As α is assumed constant here, the effects of β, depending upon p, on ψ and φ require consideration functions g and f. As $g = p - f$, the function f is of prime interest.

Despite the fairly specific restrictions that β be limited to between 0 and 1 and it be monotonically decreasing, the nature of f is still not satisfactorily explained without further restrictions. From elementary calculus we have:

$$\frac{df}{dp} = \beta + p\frac{d\beta}{dp} \quad (3)$$

As β is monotonically decreasing (in p) its derivative with respect to p is negative and thus equation (3) may or may not equal zero within the range of interest.

One possible approximation to the function β might be:

$$\beta\,(p) = Ce^{-ap}. \quad (4)$$

This parameterization is chosen purely for convenience and not as any attempt to mimic an underlying process. The constant C has no biological significance *per se*, but does yield the proportion of missed positives as the prevalence approaches zero. The other parameter, a, is assumed to be non-negative and thus the values of $\beta(p)$ will decrease as prevalence increases. This would be the case where higher prevalence reflected higher intensities of infection and increased egg loads in the stool. For larger values of a the drop in β is more pronounced. Figure 1 presents four such curves with $C = 0{\cdot}9$ for all and a changing. The line for $\beta = 0{\cdot}05$ constant is displayed as well. Despite the lack of a definite biological basis for such a choice, it is felt these examples will adequately display the relevant properties of allowing β to change with prevalence.

This effect is considerable on the function f as displayed in Figure 2. The linear increase in f for a constant sensitivity is replaced by a rapid increase to maximum followed by a decrease as prevalence increases. The 'better' diagnostic procedure (of those chosen) with the higher a produces a lower maximum, and one at a lower prevalence. The function g, on the other hand, combining both the straight line of prevalence and f shows much less change than assuming β to be constant.

In consideration of the proportion of false positives of those apparently positive, in equation (1), when sensitivity and specificity are constant, as p decreases, g decreases and $(1-p)\alpha$ increases. As this fraction therefore decreases, ψ increases to 1. Above it was noted that changing sensitivity little affected the function g and Figure 4 displays the five examples. The proportion of false positives of those apparently positive seems only slightly

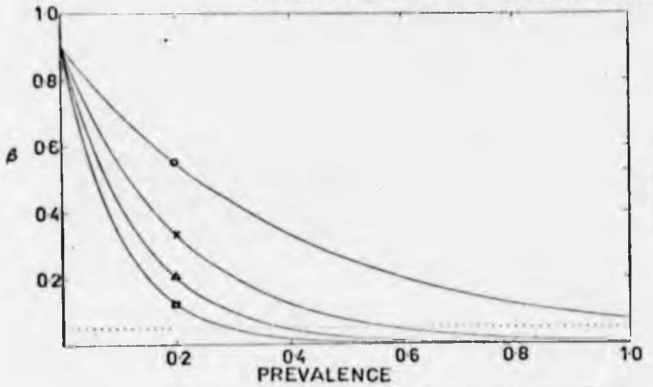

FIG. 1
Curves of β (chance of diagnostic error) as a function of prevalence. The dotted line corresponds to $\beta = 0{\cdot}05$ constant, the complete lines to $\beta = Ce^{-ap}$ with $C = 0{\cdot}9$ and $a = 2{\cdot}5$ (0), $5{\cdot}0$ (x), $7{\cdot}5$ (△) and $10{\cdot}0$ (□).

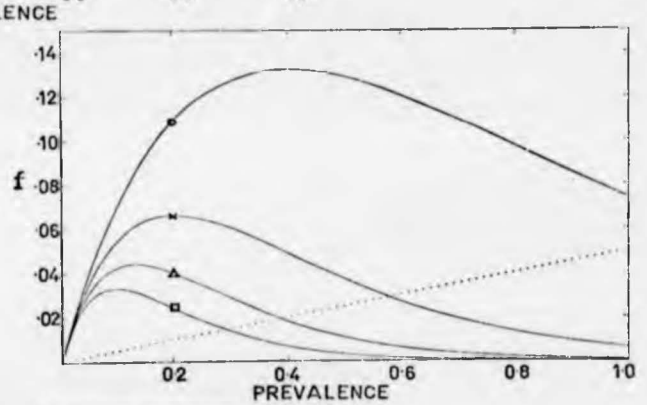

FIG. 2
Curves of $f = p\beta$ with five β alternatives described under Figure 1.

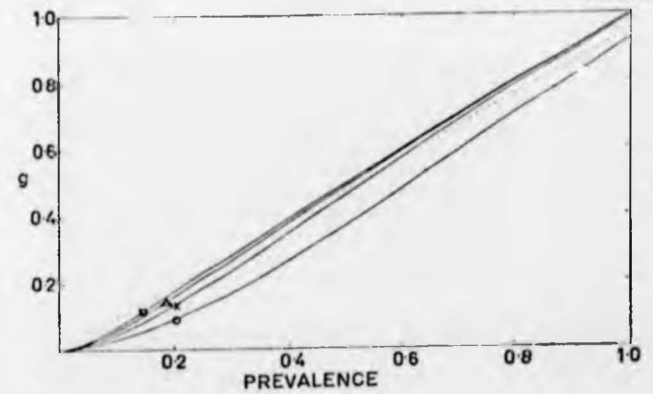

FIG. 3
Curves of $g = p(1-\beta)$ with five β alternatives described under Figure 1.

6a

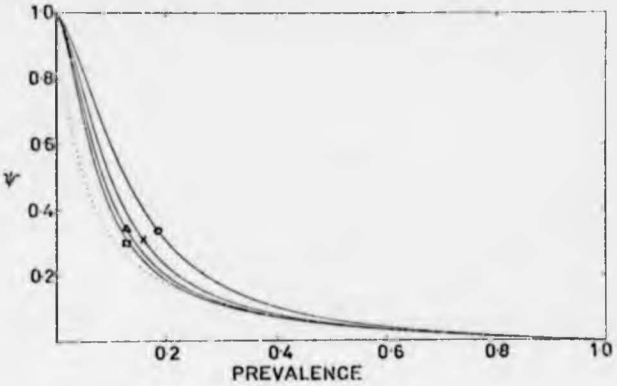

FIG. 4

Curves of proportion of false positives of false positives of those apparently positive (ψ) as a function of prevalence, and $\alpha = 0{\cdot}05$. Five curves correspond to different β's described under Figure 1.

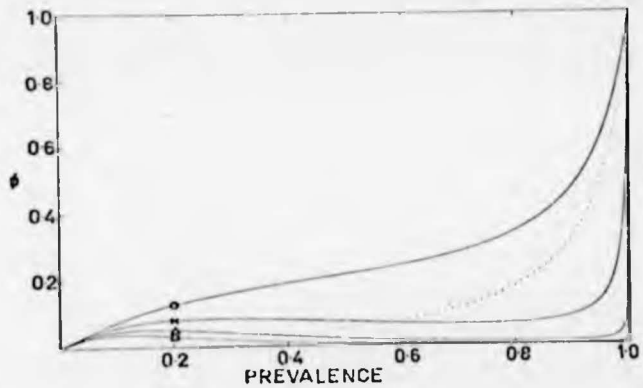

FIG. 5

Curves of proportion of false negative of those apparently negative (ϕ) as a function of prevalence. Five curves correspond to different β's described under Figure 1.

altered by having sensitivity change with prevalence.

As the equation (2) for false negatives of those apparently negative depends upon f, and as f is dramatically different under the relaxed assumption, one anticipates φ to change as well. Figure 5 confirms this, showing the five examples. As prevalence increases from zero, particularly for the higher values of α, there is a more rapid rise than for a constant sensitivity curve to a peak in some cases, followed by a decrease to lower fractions. As prevalence nears 1, there is a rapid upswing to $\varphi = 1$ at $p = 1$.

Writing $n = (1-p)(1-\alpha)$ and $A = n/f$,

one has: $$\varphi = \frac{1}{1+A}.$$

Letting p_m denote the prevalence at which f reaches its peak (here $p_m = 1/\alpha$) one can make the following heuristic observations. As prevalence increases from zero to p_m, n decreases and f increases. Thus, in this region A decreases and φ increases. After prevalence has passed p_m, there is a rapid at first, but slowing later, drop in f which approaches an asymptote greater than zero for prevalences limited to one. The numerator n, however, continues a constant drop reaching 0 at a prevalence of one. Thus A begins either to increase less rapidly or actually to decrease, with φ doing the inverse. As the prevalence nears one, while n approaches 0, f has far smaller changes, A rapidly drops and φ climbs to one.

In practical terms, as prevalence in a population

decreases, for a test of constant sensitivity, the proportion of false negatives of those truly negative drops rapidly at first but slows later in a fairly constant fashion. When β changes as in Figure 1, particularly for the 'better' procedure (higher values of a) one might expect a dramatic drop in φ at first followed by little improvement, if not a worsening rate as prevalence dropped further. In these worsening situations φ will reach a maximum and then finally drop off to zero.

As another example, it was decided to let $\beta(p)$ be given by

$$\beta(p) = Ce^{ap} + b_o. \tag{5}$$

Figure 6 represents curves for $C = 0{\cdot}9$, $b_o = 0{\cdot}05$ and $a = 2{\cdot}5$, $5{\cdot}0$, $7{\cdot}5$, $10{\cdot}0$. The line for $\beta = 0{\cdot}05$ constant is also given. Figure 7 presents the function φ for these β curves. As before, when prevalence decreases into the mid-range, for non-constant sensitivity, the situation wherein a drop in prevalence does not produce as large a drop in φ, is displayed.

CHEMOTHERAPY, SENSITIVITY AND PREVALENCE

The above results possibly explain how to view laboratory results in the face of changing sensitivity with prevalence, but more attention to epidemiological consequences of this effect is of interest.

An idealized situation is studied in which we assume there exists a completely effective drug

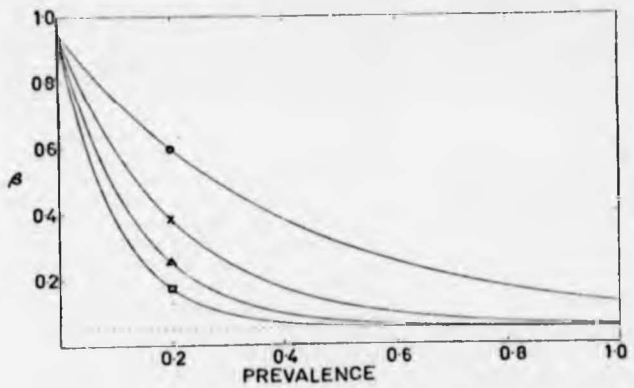

FIG. 6

Curves of β (chance of diagnostic error) as a function of prevalence. The dotted line corresponds to $\beta = 0{\cdot}05$, the complete lines to $\beta = b_o + Ce^{ap}$ with $C = 0{\cdot}9$, $b_o = 0{\cdot}05$ and $a = 2{\cdot}5$ (○), $5{\cdot}0$ (×), $7{\cdot}5$ (△), and $10{\cdot}0$ (□).

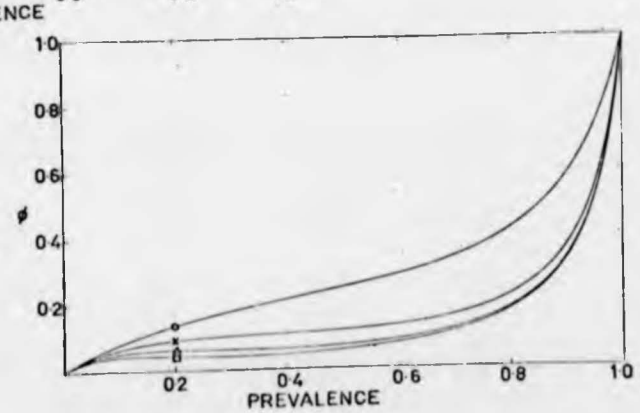

FIG. 7

Curves of proportion of false negatives of those apparently negative (ϕ) as a function of prevalence. Five curves correspond to different β's described under Figure 6.

treatment enabling a complete cure for any case positively identified. The aim of the following exercise is not to yield realistic predictions of the effect of a chemotherapy programme but rather to state a limit in the reduction of prevalence after a treatment. Under these liberal assumptions, the maximum effective drop in prevalence will be shown to be small, and purely as a result of shifting sensitivity one is advised against expecting constant spectacular reductions as after the first treatment.

Considering the population which is displayed in Table I, say treatment is given to those individuals apparently positive according to the diagnostic test. With complete cure rates, the remaining undiagnosed truly positives comprise the prevalence for the next round: $p\beta(p)$. There are now two assumptions required before repeating this process. Firstly there are assumed to be no infections, and thus the argument is only applicable to areas where transmission has ceased. This may be the case where chemotherapy is one half of a combination treatment with, say, molluscicide. Alternatively there is scope for incorporating incidence figures if they exist. A second assumption is nearly the opposite of the previous one: that there is no spontaneous loss of infection between treatments. This would most likely arise from the natural death of undiagnosed worms and can be expected to occur. One way might be to model the survival of the worms in their hosts, an area that is currently hazy but expanding at present. Alternatively one might argue that a limit based on chemotherapy treatment has been estimated, and a reduction greater than this is the fortuitous spontaneous death of several worms: it should not contribute to over-optimistic expectations of treatment effect.

Table II presents the situation after one chemotherapy treatment, where p continues to represent the prevalence of infection before treatment by chemotherapy. The effect of reducing prevalence may be to increase the proportion of true positives diagnosed incorrectly, and it becomes more and more difficult to lower the prevalence. (See Figure 1 or Figure 6.) Mathematically, the relationship between prevalences before and after treatment is given by the difference equation:

$$p_{n+1} - p_n\beta(p_n) = 0$$

Lacking an empirical curve for β by prevalence, for the sake of providing an example consider the exponential curves as drawn in Figure 1. Table III presents results for the prevalences given by the difference equations:

$$p_{n+1} - p_n \exp(-\alpha p_n) = 0 \qquad (6)$$

and

$$p_{n+1} - p_n \exp(-\alpha p_n) - b_0 p_n = 0 \qquad (7)$$

The example is far too artificial to draw any conclusions, except one can see that non-constant sensitivity of a test can lead to situations where even a perfect drug would yield rather unconvincing reductions in prevalence.

TABLE II

Distribution of individuals after one Chemotherapy treatment where β depends on the prevalence before treatment $\beta(p\beta)$ depends on the prevalence after one treatment

	Diagnosis		
	Positive	Negative	Total
Disease status			
Truly infected	$p\beta \times (1-\beta(p\beta))$	$p\beta \times \beta(p\beta)$	$p\beta$
Truly not infected	$(1-p\beta)\alpha$	$(1-p\beta)\times(1-\alpha)$	$1-p\beta$

TABLE III

Sensitivity and prevalence examples

$\beta(p)$	Prevalence (percentage) after treatment number			
	0	1	2	3	4
0·05	90	4·50	0·23	0·01	0·00
0·9 exp(−5p)	90	0·90	0·77	0·67	0·58
0·05 + 0·9 exp(−5p)	90	5·40	3·98	3·13	2·57
0·05	50	2·50	0·13	0·01	0·00
0·9 exp(−5p)	50	3·69	2·76	2·17	1·75
0·05 + 0·9 exp(−5p)	50	6·19	4·40	3·40	2·75
0·05	20	1·00	0·05	0·00	0·00
0·9 exp(−5p)	20	6·62	4·28	3·11	2·40
0·05 + 0·9 exp(−5p)	20	7·62	5·07	3·79	3·01

CHEMOTHERAPY, SENSITIVITY AND INTENSITY OF INFECTION.

While the previous section presented a mostly didactic case to show the role of changing sensitivity, it is a highly impractical approach. The use of prevalence as a statistic of interest rose in *Schistosomiasis* studies probably due to its classical role in the study of other diseases. Currently there is a strong swing to the use of intensity of infection as a measure of level of infection in a community mostly to acknowledge the importance of superinfection in the dynamics of the disease. In diagnosis as well, at an individual level, there is a stronger chance of detecting eggs and declaring a patient positive if the patient has a heavier infection than if he has a lighter infection. For the sake of possible application, one must adapt the previous section to allow sensitivity to be a function of intensity of infection.

Whereas one would ideally employ a frequency profile of a population split by the numbers of worm pairs, again on pragmatic grounds one must deal with egg output per gram of faeces. Grouping these to form manageable numbers, one might consider a population with an egg burden profile.

Corresponding to the β curve as a function of prevalence is a discrete curve of β, a function of egg burden as well. Such a curve should be deducible from study of a laboratory's results and must be assumed independent of the distribution of infection in a population.

Combining a given population's egg laying profile, a β curve of chances of escaping detection by egg output and the assumption that there is a perfect cure drug enables us to stipulate a lower limit on prevalence reduction or intensity reduction. The sum of the products of β and population at each sub-group (of a small range of egg burdens) represents the prevalence after treatment, with the individual products giving the intensity profile for the next cycle.

In reality there will be an egg burden profile obtained by survey, but there is also scope here for another form of investigation. The role of possible overdispersion of parasites among hosts has come of interest through work of Crofton (3), May (5), and Bradley and May (2). Either for a given β profile, or for a range, the combined effect of changing sensitivity with overdispersion in reduction of infection through chemotherapy might be studied. A numerical example which follows three profiles: one with parasites overdispersed (with variance exceeding mean) one underdispersed and one 'randomly' (i.e. Poisson distribution) dispersed, shows how this might be done. The egg burden curve is split roughly into eight categories attempting to classify the worm burdens. The associated limits for egg counts are entirely hypothetical, based on no empirical results and are employed for illustration only. The statistics monitored are prevalence, geometric mean infection of total population and geometric mean infection of infected population. Within each sub-group the geometric mean egg burden was used as 'mid-point' except for the last, in which 707·8135 ($=\sqrt{\{501 \times 1000\}}$) was used. Tables IV and V display the examples and the results respectively. Due to the total artificiality of these examples there is little to conclude strongly except that allowance for non-constant errors of detection can produce diminishing drops in the major indices monitored.

OTHER REMARKS

Throughout the preceding sections consideration has been made only of point estimates and no allowance for variability has been made. It is felt

TABLE IV

Sensitivity and intensity of infection examples

Category	0	1	2	3	4	5	6	7	
Egg burden (eggs/gm)	0	1–25	26–50	51–75	76–100	101–250	251–500	501+	*
β	1	·6	·4	·2	·1	·05	·01	0	
Population 1	134	312	312	173	57	11	1	0	0·75
Population 2	273	354	230	100	32	8	2	1	1·01
Population 3	429	192	111	77	54	39	28	20	2·42

* Ratio of $\sigma^2/\bar{x}$ for category numbers.

TABLE V

(a) Decrease in prevalence (per cent) after treatments

Treatment	Population 1	Population 2	Population 3
0	86·6	72·7	52·1
1	35·3	32·8	18·3
2	17·0	16·9	9·1
3	8·9	9·2	4·9
4	4·9	5·2	2·8

(b) Decrease in (geometric) mean worm burden of entire population

Treatment	Population 1	Population 2	Population 3
0	14·14	7·44	5·27
1	2·51	2·16	1·56
2	1·48	1·43	1·21
3	1·20	1·20	1·10
4	1·10	1·10	1·05

(c) Decrease in (geometric) mean worm burden of infected population

Treatment	Population 1	Population 2	Population 3
0	21·31	15·82	28·85
1	13·55	10·48	11·34
2	10·00	8·22	8·19
3	8·12	7·02	6·88
4	7·02	6·31	6·19

that for any such study, all results will depend most heavily upon the errors associated with estimating the β curve. Estimation of this will not be based on any simple error formulations particularly when one is dealing with sampling variations within a stool, between stools for one individual and between individuals in a population. Resolution of this will take considerable and careful study.

In assessing the effect of a chemotherapy programme, while cure rate is one means of evaluation, attention must be paid to the mean reduction of the number of eggs after treatment.

Lacking all the realistic restrictions necessary to apply such a method, it is fairly easy to generalize the situation described in the last system to allow for imperfect cures and possibly model the loss of infection slightly more accurately in a population. This would be an application of Markov Chain and while it would be expected to predict the loss of infection there would be no attempt to understand the transmission of the disease. From one period to the next, separated by a treatment, the proportion of people dropping from one egg burden category to another would be the product of the chance of detecting the infection and the proportion of those treated in the original category that drop to the second category (assumed above to be uninfected) after drug therapy.

Lastly it should be noted that once formal models such as that of Näsell and Hirsch (6) are applied to large control programmes, incorporation of diagnostic imperfection may provide fine tuning to describe some results.

CONCLUSION

The prime aim of this report was to investigate some epidemiological consequences of a test which had a non-constant sensitivity. Traditionally, an investigation of the behaviour of a diagnostic test involves consideration of the false positive (or negative) rate of those apparently positive (or negative). Specific conclusions on a general sensitivity curve were unavailable, but a moderate parameterization indicated that where β decreased in higher prevalences, as prevalence dropped in a population, the proportion of false negatives of those apparently negative could not always be expected to decrease as when sensitivity was constant.

The dynamic role of this effect was explored with specific reference to chemotherapy (or a combination treatment with chemotherapy) as a means of eliminating *Schistosomiasis* infection in a population. Optimistically, assuming a perfect cure rate, one can anticipate the best fall in prevalence due to the drug therapy. This is not so much to predict the exact drug effect, but rather to avoid misinterpreting small reductions as treatment failure when such may result from diagnostic imperfection.

Stipulating sensitivity to be a function of prevalence is questionable in practical terms, as the test will depend more on the intensity of infection. The relationship between prevalence and intensity of infection is not yet satisfactorily resolved. Thus the procedure was adapted to deal with measurable quantities: egg burdens. Again there is scope for suggesting a best possible reduction resulting from treatment and avoiding disappointment resulting from low, apparently unimportant changes. As well there is the possibility for investigating the role of diagnostic imperfection and parasite dispersal within hosts.

It is concluded that the role of a non-constant sensitivity warrants further thought and the analysis of large-scale investigations employing chemotherapy might benefit from consideration of diagnostic imperfection as a factor influencing effectiveness. Lastly the true empirical nature of the β profile is of prime importance. Further development of these considerations should continue once

this is estimated and proper consideration paid to the nature of errors.

ACKNOWLEDGEMENTS

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TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, VOL. 72, No. 2, 1978

On Macdonald's model for schistosomiasis

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Summary

An attempt is made to reconstruct the specifics of the model in Macdonald's 1965 paper based on some manuscripts. The resulting model is not conclusive as discrepancies occur between this formulation and Macdonald's results. Assuming the formulation is adequate, the values of parameters yielding Macdonald's standard situation are provided. A way of studying the equilibrium behaviour of the model is outlined. The mathematical nature of the properties observed by Macdonald is studied. The model is altered to admit aggregated distributions of worms in hosts and to permit different death rates of infected and uninfected snails. The dynamics are found to depend strongly on the death rate of infected snails.

Introduction

The first published model of the disease schistosomiasis was by HAIRSTON (1962) who employed a life table approach. This was followed up by subsequent work (e.g. 1965) along the same theme. In 1965, Professor George Macdonald published a model in many aspects not unlike his work in malaria. The paper served to stimulate more thought into the dynamics of this disease and since then numerous other models have been proposed.

Macdonald's work was characterized not only by a profound understanding of the biological behaviour of the transmission and an impressively capable mathematical outlook, but also with the great advantage of being able to wed these abilities. Any attempt to model the entire cycle of such a disease will necessarily call on gross simplifications. It is felt that Macdonald made assumptions that many without his experience would fail to observe at present and it would be an advantage to study these.

NÅSELL & HIRSCH (1973) have since produced a model in many ways quite similar to Macdonald's, but with a much more formal mathematical basis. It would be an advantage to compare such a model with Macdonald's to see if their modifications considerably improve upon Macdonald's work. Doubtless future models would gain as well by such a comparison.

Unfortunately the article outlining Macdonald's model was unspecific as to the precise relationship of his factors to the dynamics. Furthermore, Macdonald died in 1967 before the work he and Hairston pioneered aroused the interests of others. Some of Macdonald's papers are still held by the Ross Institute, and it was hoped that a study of these might yield some insight into his methods of approach.

Formulation of Macdonald's model

The basic mathematical features of Macdonald's model are sketched out in the appendix to his paper. His aim was to consider four factors influencing the dynamics. The four factors involved: the level of contamination by humans, the number of snails, the exposure of humans to infected water and the longevity of the schistosome in the human host. Conclusions were based on the altered dynamics resulting from the change of a factor. The precise use of the four factors was unfortunately not given, an omission particularly affecting subsequent modellers wishing to compare their work with this model. The complicated nature of some factors, for example snails, has hindered work trying to derive the model from the published results. Most of the following model description is gleaned from Professor Macdonald's manuscripts. An impression one quickly forms is that the final model is the result of investigations of other forms of the model. Thus manuscripts alluding to similar aspects at times were not identical, Macdonald having chosen a more acceptable alternative. Notation is kept as close to the original paper as possible.

In a human population of P people, there is a mean worm load of m worms, of which $a(m)$ are paired. The function $a(m)$ was given by Macdonald's equation (7)*, i.e.

$$a(m) = 1 - e^{-m}\left\{1 + \left(\frac{m}{1} + \frac{m^2}{2}\right)\frac{2!}{1!1!2^2} + \left(\frac{m^3}{3!} + \frac{m^4}{4!}\right)\frac{4!}{2!\,2!\,2^4} + \cdots\right\}.$$

NÅSELL & HIRSCH (1973) have noted the useful equivalent form of this equation:

$$a(m) = 1 - e^{-m}\left\{\sum_{k=0}^{\infty}\frac{1}{k!\,k!}(\tfrac{1}{2}m)^{2k} + \sum_{k=0}^{\infty}\frac{1}{k!\,(k+1)!}(\tfrac{1}{2}m)^{2k+1}\right\}$$

$$= 1 - e^{-m}\{I_0(m) + I_1(m)\} \qquad \{1\}^*$$

where $I_0(m)$ and $I_1(m)$ are modified Bessel Functions of orders zero and one respectively. The P people are uniformly distributed along a riverbank L metres long. Within the complex are evenly dispersed snails with a density of S snails per metre,

* Numbers of Macdonald's equations in parentheses
Number of present author's equations in braces

there being thus SL total snails. On any day each person enters the water E times and both contaminates the water and is exposed to further infection. The determination of the number of ova released per entry per person was an inconsistency in the manuscripts.

One method of treating this was to assume that the probability of a schistosome dying per day was r and each paired female produced e eggs in her lifetime. By assuming the survival of schistosomes is exponential, the mean lifetime of a worm is:

$$-\frac{1}{\log_e(1-r)} \simeq \frac{1}{r} \text{ for } r \text{ near } 0.$$

To produce e eggs in a lifetime a paired female must average e/mean lifetime or er eggs daily. Of the er eggs daily produced, a fraction k_1 of these were viable and reached the water per entry. Incorporated in the constant k_1 would be a factor of one half as the fraction of paired worms which are ova-producing. The other approach does not involve r and simply claims z_1 eggs are shed per day and (k_1z_1) viable eggs per entry are introduced to the water.

Of the $PE(k_1z_1)ma(m)$ miracidia daily introduced into the stream, only a fraction succeed in penetrating snails. This is calculated using a Poisson assumption for the distribution of successful infections as:

$$1 - e^{-0.1s}, \tag{2}$$

(On page 504 of the original article, this equation number (11) was misprinted with a 5 for an S.)

The number of successful miracidia per snail daily is thus:

$$\frac{PE(k_1z_1)(1-e^{-0.1s})\,ma(m)}{SL} = Bma(m). \tag{3}$$

The steady state argument to calculate the infection "rate" (or rather proportion) of snails infected is the same as in the appendix to Macdonald's (1957) malaria model. If p is the probability of a snail surviving one day, and the survival function is assumed to be exponential, then the proportion of snails infected is given by equation (12) of Macdonald:

$$\frac{Bma(m)}{Bma(m) - \log_e p}, \tag{4}$$

As the long prepatent period in snails may affect the dynamics of transmission, the proportion of snails which are actively releasing cercaria is:

$$\frac{p^n Bma(m)}{Bma(m) - \log_e p} \tag{5}$$

where the prepatent period is assumed to be fixed at n days.

It is unfortunate that Macdonald's discussion failed to note explicitly that allowance had been made for the prepatent period.

The determination of the inoculation rate in humaas employs several distributional assumptions. Each patent snail daily releases z_2 viable cercariae, an assumption that was constant in all manuscripts found. The probability of a cercaria successfully penetrating a prospective host entering the same metre of river is k_2. As there are z_2/L cercariae per metre from one snail, and E/L entries per person per metre per day, then there are

$$E(k_2z_2)/L \tag{6}$$

penetrations per person daily from one patent snail for the entire complex. The inoculation rate per person in man is thus:

$$h = \frac{SPE^2(k_1z_1)(k_2z_2)p^n(1-e^{-0.1s})\,ma(m)}{PE(k_1z_1)(1-e^{-0.1s})\,ma(m) - SL\log_e p} \tag{7}$$

$$= \frac{ABma(m)}{Bma(m) - \log_e p} \tag{8}$$

where

$$A = p^n(k_2z_2)SE. \tag{9}$$

On allowing for the death rate of worms, one has Macdonald's differential equation (15)

$$\frac{dm}{dt} = \frac{ABma(m)}{Bma(m) - \log_e p} - rm. \tag{10}$$

Parameterization

In several places in the original paper some parameter values are given. Furthermore a listing of the computing program used in Macdonald's original work has been discovered. The listing contained the program itself, coded in EXCHLF, a high level language for the Atlas machine used for the calculations, and a brief description of the input parameters.

The method of approximating the curve of m(t), where t is time, was a first order approximation, essentially a difference equation approach. The mean worm load was daily calculated from the previous day's values, i.e.

$$m(\tau+1) = m(\tau) + \left.\frac{dm(t)}{dt}\right|_{t=\tau} \tag{11}$$

Table I attempts to summarize the values entered to the computer program. The first three columns are duplicated from writing on an original listing. Seven values were entered for each run and those corresponding to the "standard" population are provided. The column headed "Macdonald's parameters" is as found in the sheet. The entry corresponding to Y_1 was one source of the discrepency relating to schistosome egg laying mentioned above. The last column, it is believed, is the proper description.

Table I—Input values and parameters copied from Macdonald's computer listing

Name	"Standard" Population	Macdonald's Parameters	Suspected Interpretation
Y_0	0·015	$(k_2z_2)E$	$(k_2z_2)E$
Y_1	1·25	$(k_1cr)PE$	$(k_1z_1)EP/L$
Y_2	0·95	p	p
Y_3	0·001	r	r
Y_4	0·1	m(initial)	m(initial)
Y_5	25	n	n
Y_6	5	S	S

The main parameters A and B were calculated by

$$A = Y_0 \times Y_6 \times Y_2{}^{Y_5} \qquad \{12\}$$

$$B = \frac{Y_1 \times (1 - e^{-0.1Y_6})}{Y_6} \qquad \{13\}$$

and the standard values are 0·02 and 0·1 respectively.

The mean life span of schistosomes is given as three years, or approximately 1,000 days. Thus, with exponential survival the probability of death in one day is 0·001, the value for r. The value of S was given in the paper as five snails per metre.

The relationship of Macdonald's four factors: snail, contamination, exposure and longevity to the model parameters and the input variables to the computer program remains to be explained.

The snail factor was clearly S and was investigated by altering Y_6. Runs were made with the standard value of 5 and then with Y_6 either doubled or reduced to one fifth or one fifteenth to reproduce the figures in the original text.

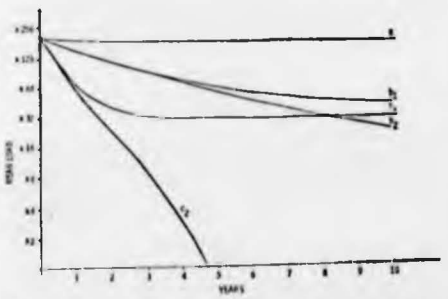

Fig. 1. Compare to Macdonald's figure three. In a the contamination factor is reduced to one fifth. For the exposure factor, b_1 represents a reduction to one fifth of Y_0 while b_2 represents Y_0 and Y_1 together. The former matches Macdonald's curve B. Curve c_1 investigates the longevity factor by reducing (to one fifth) Y_3 alone, while Y_3 and Y_2 were changed for c_2. The former matches Macdonald's curve c.

Contamination is equally clear: the parameter k_1 is altered by changing the value of Y_1. The standard value of Y_1 was likewise adjusted to produce the published diagrams.

The treatment of the exposure factor seems ambiguous as E, the natural condidate, appears in two parts of the model. This is involved both in contamination and in human inoculation arguments. Thus either variable Y_0 alone might be adjusted or both Y_0 and Y_1 together. (Adjusting Y_1 alone would be identical with contamination considerations above.) Both approaches were attempted, and it was found that Y_0 alone best reproduced Macdonald's results. Fig. 1 attempts to mimic Macdonald's figure three, and a similar result was observed in trying to duplicate Macdonald's figure two. It is thus presumed that k_2 was considered to be the exposure factor, and the choice of wording for E was possibly misleading.

One major inconsistency in the manuscripts was the handling of r, particularly in determining the daily egg production. This is clearly the longevity factor. The standard value was 0·001, and a reduction of longevity to one fifth involves changing the mean life span from about 1,000 days to about 200 days (approximately six months). Thus r is increased to 0·005. Runs were made thus changing either Y_2 or both Y_6 and Y_3 and are displayed in Fig. 1. It is concluded in comparing this with Macdonald's figure three that Y_3 alone was the longevity factor, and the (k_1z_1) argument in egg production was used.

Table II—Input parameters and Macdonald's factors

Factor	Input Parameter
Exposure	Y_0
Contamination	Y_1
Longevity	Y_3
Snails	Y_6

Table II summarizes the factors and input parameters. From these considerations one can reproduce all of Macdonald's figures except his figure four. The concept of a breakpoint and the properties ascribed to it in the text pertinent to the figure are observed, but the numerical values quoted do not bracket the breakpoint for either contamination or snails. Fig. 2 demonstrates the

effect of reducing longevity to one fifth and then lowering the contamination. A reduction of contamination to two thirds does not lead to eradication, while further reduction to three fifths does.

This inability to reproduce figure four of Macdonald's must necessarily leave the above statement of the model open to doubt.

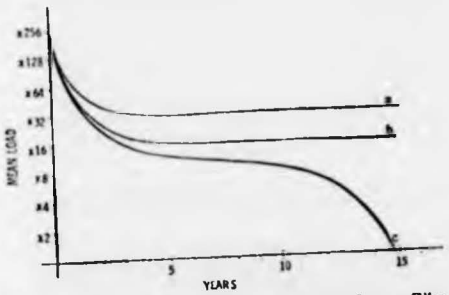

Fig. 2. Compare to Macdonald's figure four. The properties of the breakpoint hold, but parameters differ in this formulation. Longevity is reduced to one fifth alone for a with $Y_0 = 0{\cdot}015$. Then Y_0 is further reduced to 0·010 (curve b) and 0·009 (curve c).

The breakpoint and equilibrium populations

Macdonald investigated the nature of the equilibrium situation and breakpoint of his model by numerical integration of the differential equation. The specification of the model has permitted another method of investigating these properties to be derived.

In the equilibrium situation, the derivative dm/dt is equal to zero. The equilibrium mean worm load is then given by:

$$m = \frac{A}{r} + \frac{\log_e p}{Ba(m)}. \qquad (14)$$

As the paired proportion a is a function of m, this must be solved iteratively. The function a is at most one, and thus Macdonald observed in his equation (16) that an upper limit Lm of the equilibrium mean worm load is

$$L_m = \frac{A}{r} + \frac{\log_e p}{B}. \qquad (15)$$

Rather than solve (14) for m, solve it for a and consider the function:

$$a^*(m) = -\frac{r \log_e p}{B(A - rm)}. \qquad (16)$$

Whenever the values of this rectangular hyperbola correspond to the pairing function of equation (1), the value of the derivative is zero.

To investigate any parameterization of Macdonald's model, consider two curves. The first or "pairing" curve is completely independent of the model's parameters, and plots Macdonald's pairing curve for $a(m)$.

The second, or "parameter" curve, is the rectangular hyperbola given by (16) and specified by the particular parameters under investigation. Fig. 3 presents three model curves corresponding to the three possible situations.

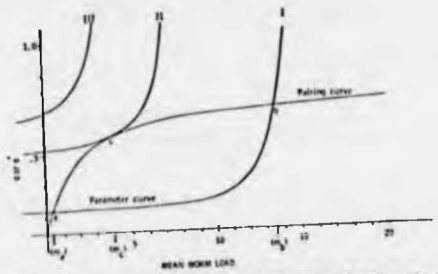

Fig. 3. Parameter and Pairing Curves. In situation I a stable population exists with breakpoint at m_a and equilibrium mean load at m_b. In situation II an (unlikely) population may occur but is unstable. In situation III no population can be supported.

It can be shown that where the parameter curve drops below the pairing curve, the value of the derivative dm/dt is greater than zero. Thus for curve I in Fig. 3, between m_a and m_b, the population increases. Where the lines cross at m_a and m_b the derivative is zero, and elsewhere the derivative is negative. Any complex starting with a mean worm load greater than m_b will decrease to m_b where it will be stable. Any mean worm load between m_a and m_b will increase to m_b. Any mean worm load below m_a will die out. Worm loads starting on m_a and m_b will remain there, but a slight disturbance will not affect m_b, yet will either lead to eradication or growth to m_b for populations at m_a. The value m_a is an unstable equilibrium point corresponding to Macdonald's breakpoint, and the value m_b is the equilibrium mean worm load: a stable critical point.

In situation II of Fig. 3, when the model curve and parameter curve only touch, the corresponding mean worm load is an unstable equilibrium. There is a theoretical justification for a population existing at this mean worm load m_c but even the slightest shift will lead to eradication. Such a situation is thought to be unlikely in any natural setting.

Lastly in curve III of Fig. 3, there are no intersections of the two curves, and thus no population can be supported for this set of parameters.

Fig. 4 presents this way of investigating the situation for Macdonald's figure one. The intersection at b corresponds to the equilibrium mean worm load of m_b. The asexual counterpart in this interpretation is to let the horizontal line of $a = 1$ be the pairing curve. While the intersections b

and c are separate, the corresponding equilibrium mean worm loads are close together, which is also noted in Macdonald's figure one.

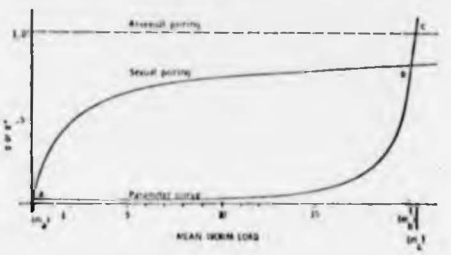

Fig. 4. Parameter and Pairing Curves. Macdonald's standard population is used as an illustration.

There is a visual manner of noting the phenomenon of a "washout" of Macdonald's breakpoint. Control of the disease in any endemic situation can take two strategies: either by lowering the mean worm load m in a manner independent of changing the parameter values of A, B, p or r; or by adjusting the parameters themselves, shifting the intersections referred to above. A successful control scheme will reduce the region where the parameter curve lies below the pairing curve. One would aim to raise the breakpoint to above the value of m observed. In such a case however, an influx of worms from outside the complex may help re-establish an endemic situation. However, a truly beneficial control campaign will alter the parameter curve to take the form of III in Fig. 3 where there is no possibility of sustaining a population. This is the "washout" of the breakpoint.

Some of the properties of the model are obtained by considering the possible intersections of the two curves. The rectangular hyperbola has a y intercept at

$$a^* = -\frac{r \log_e p}{AB} \qquad \{17\}$$

and an asymptote at

$$m = A/r. \qquad \{18\}$$

As the pairing curve is necessarily between zero and one, any situation with an intercept given by {17} which is greater than one obviously cannot produce an endemic situation. The equilibrium, in cases where it does exist cannot be greater than the value given by {18} and the amount less than this is shown by equation {14}.

The rather complicated form of the pairing curve rules out any rapid mathematical calculations of the values of the breakpoint and equilibrium load. Macdonald gives an approximation to his function. An alternative is to observe that the pairing curve is itself not unlike a rectangular hyperbola. An approximate form is given by

$$a(m) = \frac{0{\cdot}88m}{m + 1{\cdot}73}. \qquad \{19\}$$

The values were determined to give a reasonable fit to values of m between 0 and 15. As m gets larger, the error becomes greater than 0·007.

With this approximation the intersections of the two curves can be estimated. The values of m which satisfy the quadratic equation:

$$0{\cdot}88rBm^2 - (r \log_e p + 0{\cdot}88AB)m - 1{\cdot}73r \log_e p = 0 \qquad \{20\}$$

will correspond to the breakpoint and equilibrium. Let

$$\left.\begin{aligned} C_2 &= 0{\cdot}88rB \\ C_1 &= -r \log_e p - 0{\cdot}88AB \\ C_0 &= -1{\cdot}73r \log_e p . \end{aligned}\right\} \qquad \{21\}$$

The discriminant of {20} is then:

$$\Delta = C_1^2 - 4C_0C_2 .$$

By studying Δ one can establish roughly if the parameter curve is like curve I of Fig. 3 ($\Delta > 0$), curve II ($\Delta = 0$) or curve III ($\Delta < 0$). (In light of the approximation, the second case would require special attention, as would any where Δ is nearly 0.) The breakpoint and equilibrium mean worm load can be approximated by:

$$\tfrac{1}{2}(-C_1 - \Delta)/C_2 \text{ and } \tfrac{1}{2}(-C_1 + \Delta)/C_2$$

respectively. As an example, the asymptotic mean worm load for the standard population is exactly 20·171 and is approximated as 20·161.

Properties of Macdonald's model

Two major conclusions of the paper were that both snail and exposure factors had similar influence, and that contamination (sanitation) had little over-all effect.

The similarity in effects of snail and exposure factors can be traced to the assumption that the proportion of successful miracidia depends on the number of snails given by equation {2}. An expansion in the determination of B gives:

$$1 - e^{-0{\cdot}1S} \simeq 0{\cdot}1S - 0{\cdot}005S^2 + 0{\cdot}0001667S^3 - 0{\cdot}0000041667S^4. \qquad \{22\}$$

The effect of doubling the exposure factor is to double the value of A but leave B, p and r unchanged. Doubling the snail factor Y_s also doubles A but has very little effect on B for the values of Y_s used (maximum of S = 10) while leaving p and r unchanged. Thus, as B in this formulation is relatively insensitive to S, both snail and exposure factors affect A similarly and leave the rest of the model unchanged.

The insensitivity of the model to the contamination factor is less obvious, and is mostly a result of the choice of values for parameters in the model. A way of investigating this property is to consider

changes in the equilibrium mean worm load as the various factors increase and decrease.

Figs. 5 and 6 attempt to summarize such an investigation. Fig. 5 represents the sensitivity of the model for the standard population as the expected life span of the schistosome varies about its standard of 1,000 days. At the values Macdonald selected, with chemotherapy reducing the life span to around 200 days, the model is changing rapidly and a reduction to 100 days would cause the washout or eradication of the diseases. At the standard level and above, the model is sensitive to changes in r. This can be viewed as a shift to higher values of m of the asymptote to the parameter curve as r decreases.

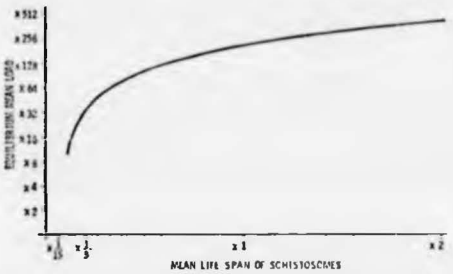

Fig. 5. Sensitivity of the model to longevity. The change of the equilibrium mean worm load for Macdonald's standard population as the longevity of the schistosome changed from the standard value of 1,000 days.

Two sets of curves for the other three factors are displayed in Fig. 6. For each of contamination, snail and exposure factors, the relationship is traced for longevity at its standard value r = 0·001 and reduced to one fifth by a chemotherapy campaign r = 0·005. Not surprisingly the results for snail and exposure factors are quite similar. The effect of chemotherapy is most noticeable in the change of the point of washout, and the equilibrium mean worm loads at the same levels of each factor. In particular the population is supported when factors are reduced to one fifth their standard level when r is 0·001, but chemotherapy r = 0·005 shifts the washout level to the other side of one fifth. This was shown by Macdonald's figures three and five respectively. Around the standard level for both factors, the equilibrium mean worm load is sensitive to changes, again possibly viewed as similar changes in the factor A for the asymptote of the parameter curve.

The results for contamination are different: visual inspection confirms that large changes in the value will produce very small changes in the equilibrium value. It is interesting to note that in Macdonald's figure five, contamination was reduced to one fifteenth and little change in the equilibrium mean worm load was observed. Fig. 6 for r = 0·001 shows that this reduction is just on the rapidly changing part of the curve. The effect is obscured possibly by use of a long time scale, by a ratio scaling and by the fact that all other populations died out. A further reduction to one-twentieth would have produced quite different results. As contamination does not affect factors A or r, the asymptote for the pairing curve is unaltered and only the curvature of the curve is changed; thus one might expect this insensitivity.

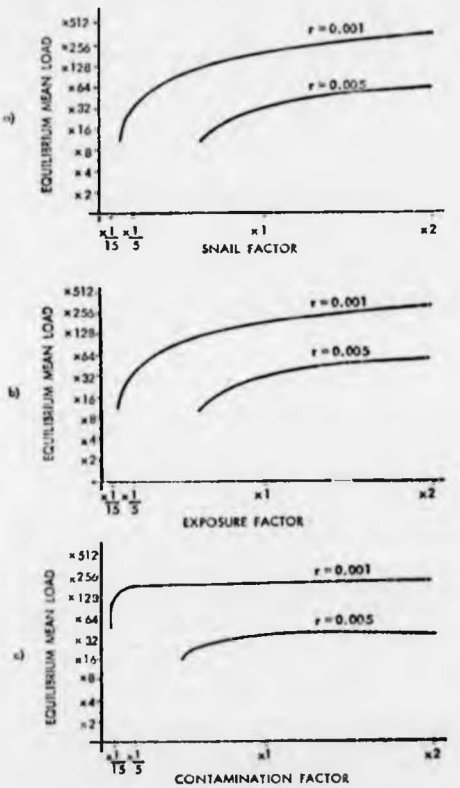

Fig. 6. Sensitivity of the model to snails (a), exposure (b) and contamination (c) for the standard situation r = 0·005. For the standard values, see Table II.

For biological interpretations it is of interest to compare the effect of contamination on the proportion of snails infected. It is important to discriminate between the proportion of snails infected given by (4) and those patently infected given by (5). The appropriate proportions are shown in Table III. It is clear that the actual

Table III—The effect of changing contamination on the equilibrium proportion of snails infected and patent

		r = 0·001		r = 0·005	
		Infected	Patent	Infected	Patent
Contamination	× 1/5	·85	·23	—	—
	× 1/2	·94	·26	·47	·13
	× 1	·97	·27	·78	·22
	× 2	·98	·27	·90	·25

infection rates in snails were quite high and the proportions of patent snails were strongly dependent on the choice of n, the length of patency.

Some assumptions relaxed

An understanding of the specifics of Macdonald's model has facilitated the investigation of slightly altered situations.

The assumption that worms are distributed according to a Poisson distribution amongst hosts has been studied lately by BRADLEY & MAY (1977). The effects of aggregation on the dynamics can be studied readily by means of the intersection of parameter and pairing curves described above.

Rather than assume a Poisson distribution, consider the situation where worms follow a negative binomial distribution with males and females equally likely. This distribution admits one parameter which describes the "aggregation" or clumping wherein the variance exceeds the expectation. Lower values of k, the clumping parameter, represents situations farther removed from Macdonald's assumption, and as k increases the Poisson distribution is approached. The effect of changing k is to alter the shape of the pairing curve leaving the parameter curve unchanged.

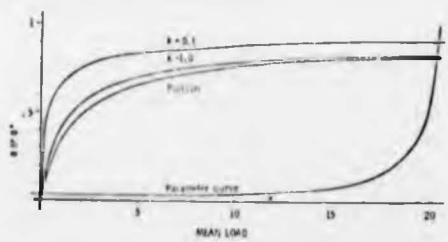

Fig. 7. Clumped distribution of worms in hosts. The standard parameter hyperbola is superimposed to show the effects on breakpoint and equilibrium mean loads.

Fig. 7 represents the standard parameter curve and various pairing curves from Poisson to highly aggregated (k = 0·1). This figure was obtained by using an altered form of Macdonald's equation 7. Where the mean worm load is m and clumping is k, by setting

$$P = \frac{k}{k+m} = 1 - q$$

the proportion of worms paired is given by:

$$1 - \frac{p^k}{m}\left\{(0 + kq)1 + \left(\frac{(k)_1}{1!}q^2 + \frac{(k)_2}{2!}q^3\right)\frac{2!}{1!\,1!\,2^2} + \ldots\right\}$$

where $(k)_i = k(k+1)\ldots(k+i-1)$.

Further elaborations along these lines are to be found in MAY (1977). Strict observations depend greatly on the specific parameter curve, but broadly speaking the greater the aggregation, the better the chances of an endemic situation occurring (a better opportunity for the intersection of the curves) and the lower the value of the breakpoint. This is merely one example; there is scope for considering several other forms of pairing curves.

Macdonald speculated (page 493) that the effects of infection on snail mortality would not qualitatively alter the model. In the appendix, the model to allow for this is shown to be

$$\frac{dm}{dt} = \frac{(k_2 z_2) S E p_i^n B m a(m)}{B_r a(m) - \log_e p_u} - rm \qquad \{23\}$$

where p_i is the proportion of infected snails dying in one day and p_u is the proportion of uninfected snails dying in one day (where survival is assumed to be exponential).

The dependence on the proportion of patent snails is strongly affected by changes in p_i (as it is used to the nth power) whereas changes in p_u tend to have less effect. For example three situations are summarised in Fig. 8 and Table IV. The parameter A of the previous model in {9} can be thought of as:

$$A_i = p_i^n (k_2 z_2) P l^2 \qquad \{24\}$$

and the pairing and parameter curve approach is still relevant. Clearly changes in p_u do not affect the asymptote of the parameter curve and one might not expect large changes in the equilibrium

Table IV—Summary statistics for model with different death rate of infected snails

p_u	p_i	Asymptote for Parameter curve	Breakpoint mean worm load	Equilibrium mean worm load
0·95	0·95	20·80	0·052	20·17
0·95	0·93	12·22	0·090	11·54
0·97	0·95	20·80	0·030	20·43

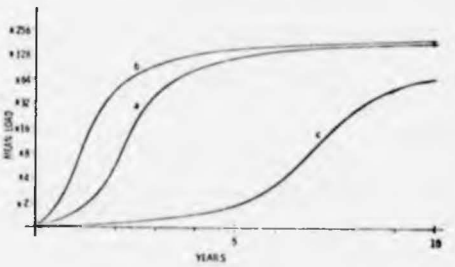

Fig. 8. Allowing for a different death rate of infected snails. Curve a is the standard case with $p_i = p_u = 0{\cdot}95$. In b uninfected snails die later: $p_i = 0{\cdot}95$, $p_u = 0{\cdot}97$. For c infected snails die earlier: $p_i = 0{\cdot}93$, $p_u = 0{\cdot}95$.

mean worm load. However as A_1 is greatly affected by changes in p_i (as the latter is raised to the nth power) then the asymptote to the parameter curve will change considerably. Table IV suggests that the shorter the lifespan of infected snails, the higher the breakpoint and lower the equilibrium load. Macdonald's observation concerning the qualitative nature of the model therefore holds, but the accurate determination of p_i appears to be imperative.

Conclusions

To facilitate comparisons of other models to Macdonald's, an attempt has been made to reconstruct the specific nature of the model. Some ambiguities exist, particularly concerning the longevity factor and the exposure factor. By considering various alternatives an attempt was made to mimic Macdonald's figures two and three. By this means, a formulation was suggested as summarized in Table II. As a result, four of Macdonald's five figures can be reproduced. It has not been possible to duplicate Macdonald's fourth figure although the properties displayed by the illustration are appropriate.

An alternative technique for investigating the breakpoint and equilibrium properties of the model was outlined. This involved a study of the intersections of two curves: the pairing curve and the parameter curve. The pairing curve, given by Macdonald's equation (7), was crudely approximated by a rectangular hyperbola to provide rough techniques (not involving iterative calculations) of studying the intersections.

An attempt was made to investigate some of the mathematical properties yielding Macdonald's biological findings. The similarity between the snail and exposure factors was traced to the insensitivity of the inoculation rate for snails to the number of snails. The sensitivity of the equilibrium mean worm load to the parameter values Macdonald employed was studied. It was learnt that the equilibrium mean load curve was particularly flat in the region Macdonald was studying for the contamination factors.

Two assumptions were relaxed. It was demonstrated that the curve intersection way of studying the model could be employed where worms were clumped in hosts, rather than distributed according to a Poisson distribution. The effect of clumping was to increase the chances of a stable population resulting. Allowance for a different death rate for infected snails was made. The model is not qualitatively different from Macdonald's original but the dynamics and steady state situation are found to be particularly sensitive to this death rate.

Acknowledgements

I wish to thank both Professor P. Armitage and Professor D. J. Bradley for their interest and advice. The work was supported by a grant from the Rockefeller Foundation.

Appendix

The derivation below of the proportion of infected snails does not follow Macdonald but rather is based on an approach of SHIRLEY (1971).

Assume the proportion of infected snails dying in one day is p_i, while the corresponding proportion for uninfected snails is p_u. Let the distribution of time to infection for a snail be exponential with parameter Bmα(m).

$$\Pr(\text{infected snail dies at } t) = \gamma_i e^{-\gamma_i t} dt \qquad \text{(A1)}$$

$$\Pr(\text{uninfected snail dies at } t) = \gamma_u e^{-\gamma_u t} dt. \qquad \text{(A2)}$$

Then one has:

$$p_i = e^{-\gamma_i} \quad \text{or} \quad \gamma_i = -\log_e p_i \qquad \text{(A3)}$$

$$p_u = e^{-\gamma_u} \quad \text{or} \quad \gamma_u = -\log_e p_u. \qquad \text{(A4)}$$

For each snail let t be the time of death and τ be the time of infection. (Snails for which $\tau > t$ will die uninfected.) The entire distribution of snails is spread across the two dimensional plane in Fig. 9. Those snails in S_1 die uninfected. Those dying in

S_2 are infected but die before becoming patent (within n days). Those in S_3 are patent before dying, and represent the proportion relevant to the model.

Each point in S_1 has the associated probability:

$$\Pr(X \in S_1) = \Pr(\text{snail dies at } t) \times \Pr(\text{snail is uninfected by } t)$$

$$= \gamma_u e^{-\gamma_u t} \int_t^\infty Bm\alpha(m) e^{-Bm\alpha(m)\tau} d\tau. \quad \{A5\}$$

The entire proportion of snails is S_1 is thus

$$\int_0^n \gamma_u e^{-\gamma_u t} \int_t^\infty Bm\alpha(m) e^{-Bm\alpha(m)\tau} d\tau dt = \frac{\gamma_u}{Bm\alpha(m) + \gamma_u}. \quad \{A6\}$$

(This proportion does not depend on the death rate of infected snails.)

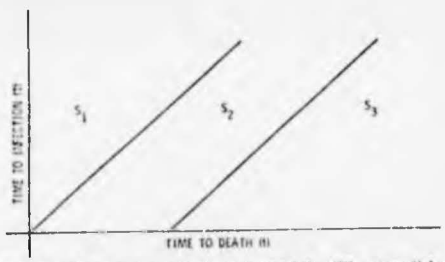

Fig. 9. Derivation of altered model. The possible outcome of snails becoming infected and dying.

Any snails lying in area S_2 will have an associated probability:

$$\Pr(y \in S_2) = \Pr(\text{alive and then infected at } \tau) \times \Pr(\text{survives a further } T = t - \tau < n) = e^{-\gamma_u \tau} Bm\alpha(m) e^{-Bm\alpha(m)\tau} \times \gamma_i e^{-\gamma_i T}, \quad T < n. \quad \{A7\}$$

The entire proportion of snails dying infected but prepatent is thus:

$$\Pr(S_2) = \int_0^n e^{-\gamma_u \tau} Bm\alpha(m) e^{-Bm\alpha(m)\tau} \int_0^n \gamma_i e^{-\gamma_i T} dT d\tau = \frac{Bm\alpha(m)}{Bm\alpha(m) + \gamma_u}(1 - e^{-\gamma_i n}) = \frac{Bm\alpha(m)}{Bm\alpha(m) - \log_e p_u}(1 - p_i^n). \quad \{A8\}$$

Any snail lying in area S_3 will have an associated probability:

$$\Pr(z \in S_3) = \Pr(\text{alive and then infected at } \tau) \times \Pr(\text{survives a further } T = t - \tau > n) = e^{-\gamma_u t} Bm\alpha(m) e^{-Bm\alpha(m)\tau} \times \gamma_i e^{-\gamma_i T}, \quad T > n. \quad \{A9\}$$

The entire proportion of snails dying patently infected is thus:

$$\Pr(S_3) = \int_0^\infty e^{-\gamma_u t} Bm\alpha(m) e^{-Bm\alpha(m)\tau} \int_n^\infty \gamma_i e^{-\gamma_i T} dT d\tau = \frac{e^{-\gamma_i n} Bm\alpha(m)}{Bm\alpha(m) + \gamma_u} = \frac{p_i^n Bm\alpha(m)}{Bm\alpha(m) - \log_e p_u}. \quad \{A10\}$$

By an argument following the simplified model in the main part of the paper one has equation {23}.

A further assumption has been made in the above integrations that $Bm\alpha(m)$ is independent of time, which is clearly inconsistent with the rest of the model. Thus the above proportions are only appropriate for conclusions concerning the steady state behaviour. In populations where m was decreasing, the above argument will overestimate the proportion patently infected and the curve for m(t) will decline more slowly then it should. In situations where m was increasing, the curve for m(t) will grow more rapidly than it should.

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