Population biology of infectious diseases: Part II

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In the first part of this two-part article (Nature 280, 361-367), mathematical models of directly transmitted microparasitic infections were developed, taking explicit account of the dynamics of the host population. The discussion is now extended to both microparasites (viruses, bacteria and protozoa) and macroparasites (helminths and arthropods), transmitted either directly or indirectly via one or more intermediate hosts. Consideration is given to the relation between the ecology and evolution of the transmission processes and the overall dynamics, and to the mechanisms that can produce cyclic patterns, or multiple stable states, in the levels of infection in the host population.

In the first part of this article we considered the dynamics of parasites among hosts (or even, occasionally, by making a crude division of the host population into susceptible, infected and immune classes, an approach that is not helpful, and a detailed description of the nature and underpinning of these equations, and their dynamical behaviour, have been expounded in detail elsewhere). A rough understanding of the relation between this system of equations for typical macroparasites with direct transmission, and the earlier set of equations (8)-(10) of Part I for directly transmitted microparasites, can be obtained as follows. First, note that the lifespan of the free-living infective stages is usually much shorter than that of the host and the adult parasite (compare Table 1). Thus the set of differential equations can be decoupled, by assuming the 'short lived' infective stages are adjusted essentially instantaneously to their equilibrium level (\(dw/dt = 0\) for any given value of \(N\) and \(P\)). This gives

\[
\begin{align*}
\frac{dN}{dt} &= (a - b)N - aP \\
\frac{dP}{dt} &= \beta w N - (\mu + b + \alpha)P - \alpha (k + 1)P^2/(kN) \\
\frac{dw}{dt} &= \lambda P - cw - \beta w N
\end{align*}
\]

Here the birth and death rates \(a\) and \(b\) are as defined in the first part of this article, as is the transmission parameter \(\beta\) (hosts acquire individual adult parasites at a rate proportional to the number of contacts between hosts and parasite infective stages, \(\beta w N\)). The parasite-induced host death rate \(c\mu\) (equivalently, depression of the birth rate) is taken to be linearly proportional to the parasite burden in a given host, at a rate \(c\mu\) per parasite. The parasites are distributed as a negative binomial with parameter \(k; \mu\) is the natural mortality rate of adult parasites; \(\lambda\) is the rate of production of infective stages by an adult parasite; and \(c\) is the death rate of these infective stages. The biological underpinning of these equations, and their dynamical behaviour, have been expounded in detail elsewhere.

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\end{align*}
\]

(where \(r = a - b\) and \(H_0 = c/\beta\)). Second, a phase-plane analysis now lays bare the properties of this pair of equations.

Three patterns of dynamical behaviour are possible\(^{14}\). (1) If

\[
\lambda - (\mu + b + \alpha) > r(k + 1)/k
\]

(6)
The parasite regulates the host population to a stable equilibrium value. The average parasite burden per host settles to
\[ m = r/\alpha \quad (7) \]

(2) If Equation (6) is not satisfied, but
\[ \lambda - (\mu + b + \alpha) > 0 \quad (8) \]
the host population continues to grow exponentially, but at a rate
\[ \rho = r - \left[ \lambda - (\mu + b + \alpha) \right] k/(k+1) \quad (9) \]
This is less than the disease-free rate, \( r \). In this case, the mean parasite burden in the exponentially growing host population settles to the value
\[ m \rightarrow (r - \rho)/\alpha \quad (10) \]

In either event, if the host population is initially below the value
\[ N_F = \frac{H_0(\mu + b + \alpha)}{\lambda - (\mu + b + \alpha)} \quad (11) \]
the parasite cannot become established \( (dP/dt < 0) \). However, as long as Equation (8) is satisfied, the host population will grow exponentially \( (at the rate \( r \)) until this threshold value \( N_F \) is exceeded, whereupon the infection will become established, either regulating the host population or at least slowing its growth rate. Furthermore, in view of the large values for the reproductive output \( \lambda \) of most helminth parasites, \( N_F \) will typically be relatively small. This expectation of commonly finding direct life cycle helminth infections persisting in low density host populations is borne out by the evidence.

(3) Finally, if \( \lambda \) is so small that Equation (8) is not satisfied, the infection can never become established \( (N_F \) is negative!)

The similarities between cases (1) and (2) here, and the results displayed in Fig. 4 of Part I, are striking. In particular, for measures of the prevalence of infection, notice the exact formal equivalence between equation (15) of Part I and equation (7), and between equation (17) of Part I and equation (10). A dissimilarity is that whereas the ability of a microparasite infection to regulate its host population essentially depends on its pathogenicity \( \alpha \) exceeding the host population growth rate \( r \) (weighted by rates of recovery, loss of immunity and so on: see Table 1 of Part I), for a macroparasite it is its net reproductive ability, \( \lambda - (\mu + b + \alpha) \), that plays a central role \( (\lambda \) is the 'birth rate'), while \( \mu \), \( b \) and \( \alpha \) are the natural parasite, natural host and parasite-induced host death rates). The macroparasitic infection can never persist if this effective net reproductive rate is not positive \( (equation \ (8)) \). The parasite will regulate the host population, or merely slow its growth, depending on whether this effective net reproductive rate \( \lambda - (\mu + b + \alpha) \) is, or is not, greater than the host reproductive rate \( r \), weighted by a factor \( (k+1)/k \) to allow for the clumped distribution of parasites. Thus equation (6) is for these directly transmitted macroparasites the analogue of the microparasite equation (13) in Part I.

**Indirect life cycles** constitute another qualitatively different kind of complication, arising when the life cycle of the parasite involves one or more intermediate hosts. This happens for both microparasites (for example, the arthropod-borne viruses or arboviruses such as yellow fever or Rocky Mountain spotted fever; the protozoan malaria species) and macroparasites (for example, schistosomes, the filarial worms causing onchocerciasis, and other roundworms and flatworms that involve dipteran, molluscan and other intermediate hosts). Malaria and schistosomiasis in human populations are the two parasites whose transmission cycles have been most fully studied and each enjoys its own independent and growing literature, both empirical and theoretical (see Table 2). Their basic dynamical character is, however, in many respects common to all parasites with indirect life cycles.

If we adopt the approach of equations (8)–(10) and Fig. 3 discussed in part I, namely dividing the host population into susceptible, infected and immune categories, we will in the simplest case have a system of six differential equations: three for the primary host \( (\) alternatively referred to as the definitive host, or final host \( \)) classes \( X, Y, Z \); three for the intermediate vector populations \( X', Y', Z' \). All existing models, however, assume the total populations of both primary host \( (N = X + Y + Z) \) and the intermediate host \( (N' = X' + Y' + Z') \) are constant, unaffected by the dynamics of the disease. This reduces the system to four equations. If, furthermore, immunity is either ignored or handled by specific assumptions about 'superinfection', the \( Z \) and \( Z' \) classes are effectively removed to give two coupled differential equations for the number of primary hosts \( Y \), and of intermediate vectors \( Y' \), that are infected. This, in essence, is the source of the classic Ross-Macdonald malaria equations, the Nasell-Hirsch Schistosomiasis model, and the Dietz\(^{20}\) arbovirus equations.

These equations have been subjected to various kinds of more refined treatment, including age structure\(^{20-24}\), immunity and superinfection\(^{17-21,23-26}\) and the use of several immunological categories of hosts\(^{26}\) (intermediate betweenFig. 3 of Part I and Fig. 1 of Part II). However, essentially all the existing work on

**Table 1** Expected lifespans of the host and parasitic stages involved in the life cycle of *Schistosoma mansoni* and *Ancylostoma duodenale*

<table>
<thead>
<tr>
<th>Population</th>
<th>Lifespan (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. mansoni</em></td>
<td></td>
</tr>
<tr>
<td>Man (primary host)</td>
<td>50.00</td>
</tr>
<tr>
<td>Adult parasite</td>
<td>5.00</td>
</tr>
<tr>
<td>Infected snails (intermediate host)</td>
<td>0.10</td>
</tr>
<tr>
<td>Cercariae</td>
<td>0.003</td>
</tr>
<tr>
<td>Miracidia</td>
<td>0.0009</td>
</tr>
<tr>
<td><em>A. duodenale</em></td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>50.0</td>
</tr>
<tr>
<td>Adult parasite</td>
<td>1.0</td>
</tr>
<tr>
<td>Free-living infective stage</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Fig. 1 Diagrammatic flow chart for a directly transmitted infection, based on a model with compartments for the number of hosts, \( N(i) \), harbouring \( i \) parasites \( (i = 0, 1, 2, \ldots) \). The model has a structure similar to, but obviously more complex than, that of Fig. 3 of Part I\(^1\).
indirectly transmitted parasites retains the assumption that the populations of host and intermediate vector are constant, not dynamically involved with the infection. Analysis of such models reveals threshold relations\(^7\text{,}20\text{,}21\text{,}27\text{,}28\) between \(N\) and \(N'\), analogous to but more complicated than the \(N_i\) of the direct life cycle models. If \(N\) and \(N'\) lie below the threshold combination, the disease cannot be maintained.

For many human, and other animal, infections by parasites with indirect life cycles, what is needed is a theory in which the populations of primary and intermediate hosts are affected, and possibly even determined, by the presence of the infection. While it may often be reasonable to treat a human primary host population as roughly constant, we believe that cases where intermediate host populations are unaffected by the prevalence of the infection will be the exception rather than the rule\(^29\). There is no formal problem in extending our dynamic models of either the 'microparasite' kind of equations (8)–(10), (Part I) or the 'macroparasite' kind of equations (1)–(3) (Part II), to encompass the added complication of one or more intermediate vector populations. Space forbids a full exposition of the emergent properties, but the main trends are indicated in the following section.

### Time scales and transmission terms

A full model for an indirectly transmitted parasite might include not only dynamical descriptions of the prevalence of infection in primary and intermediate host populations, but also additional differential equations (analogous to equation (3)) for the free-living transmission stages that carry the parasite from primary to intermediate host, and back again. For example, for schistosomiasis we could add a differential equation describing the miracidial stage (man to snail), and another for the cercarial stage (snail to man), to the usual equations for infection levels in the human and snail populations\(^30\). The reason this is not commonly done can be seen from Table 1; the dynamics of the free-living stages takes place on a time scale much shorter than the other time scales in the system that macsidial and cercarial populations can be assumed to have the equilibrium values appropriate to the prevailing conditions among human and snail populations. In just this way, we collapsed the three-equation system (1)–(3) to the two equations (4), (5).

This type of using biological insights about the time scales of various infection processes can be used to make further rough but useful approximations. For example, the time scales for processes (such as mortality rates) within the intermediate host population are typically significantly shorter than those in the primary host. Again, Table 1 testifies to this. Accordingly, we can assume that the numbers of susceptible, infected and immune intermediate hosts are adjusted to have the equilibrium values \(dX'/dt = 0\), and so on) appropriate to the current levels of infection in the primary hosts. In this way, parasitic infections with indirect life cycles can be approximately brought to a form similar to that of equations (8)–(10) in Part I for direct life cycles\(^1\).

As a concrete example, consider a grossly oversimplified model for malaria, in which 'superinfection' and mosquito latency\(^7\text{,}21\) (and immunity\(^7\text{,}26\)), are ignored. Assume also that the total mosquito population is constant; \(N' = X' + Y'\) = constant. The populations of infected humans \(Y'\), and mosquitoes \(Y'\), then obey

\[
dY'/dt = \beta Y' X' (b + a + v) Y' + \lambda Y' - \mu Y'
\]

Here \(\beta, a, v\) and \(\lambda\) (plain for humans, primed for mosquitoes) have their previous meanings; conventionally, most infected humans are assumed to recover \((\lambda > a, \beta)\), and most infected mosquitoes to die at a rate largely unaffected by the infection \((\lambda > a, v)\). The assumption that mosquito processes happen on a relatively fast time scale enables \(Y'\) in equation (12) to be determined by setting \(dY'/dt = 0\) in equation (13), leading to

\[
dY'/dt = Y(\beta\beta'NX')/(b + a + v + \lambda) - (b + a + v)Y'
\]

This is exactly of the form for a directly transmitted infection (equation 9 of Part I), except that the simple transmission coefficient \(\beta\) has been replaced by the more complicated factor \(\beta\beta'N'/(b + a + v + \lambda)\). Similarly, the Nasell–Hirsch two equation model\(^19\) for prevalence of schistosomiasis among humans and snails can be collapsed to Macdonald's\(^27\text{,}28\) single equation for prevalence in the human population.

Conversely, for humans the total population is often growing on a time scale that is long compared to the relevant time scales of even persistent infections. This is why the total population can be treated as a constant in most epidemiological models. The approximation, whereby the dynamics of the prevalence \(Y'/N\) and of the total population \(N\) are decoupled, can often be useful in discussing the transmission cycle of the infection, even though the long-term growth or regulation of the host population is affected by the presence of the infection.

Table 2 uses these ideas to attempt to give a schematic account of the relation among some of the many models, of differing degrees of complexity, that are to be found in the literature.

### Saturation of transmission terms

The transmission terms obtained in equation (14) by 'collapsing out' the mosquito dynamics of equation (13), and in equation (5) by collapsing equation (3) for the free-living infective stages of the parasite, manifest a feature that is common to all such approximate representations of complex transmission processes\(^4\text{,}5\text{,}14\text{,}21\text{,}32\). Essentially, the simple term \(\beta XY'\) for direct transmission

| In considering the dynamics of infection, only one species is involved (for example, the host species). | Host population(s) constant |
| Direct life cycles | Classical epidemiological models (refs 21, 56, 65, 67, 83–84, 87). Models for the dynamics of a parasite population within a host population of fixed size (refs 5, 88, 89). |
| Indirect life cycles | Models for schistosomiasis (refs 28, 34, 90) and for malaria (refs 17, 18, 21), considering only the dynamics within the human host. |

| In considering the dynamics of infections, two or more species are involved (e.g., primary and intermediate host, or host and parasite population). | Host population(s) a dynamic variable |
| Direct life cycles | Models similar to those for classical epidemiology, but with total host population a dynamic variable, determined by birth and death processes (refs 35, 91 and this review). |
| Direct and indirect life cycles | Dynamics of models in the compartment below but with all populations but the primary host 'collapsed out' (this review). |

| Indirect life cycles | Models similar to classical epidemiology, but with host population and free living infective stages both included as dynamic variables (ref 35). Models for dynamics of host parasite systems (refs 3, 4, 7, 8, 14, 35), sometimes with dynamic aspects of free-living infective stages also included (refs 3, 4). |
| Indirect life cycles | Any of the models in the compartment to the left, but with the total host populations treated as dynamic variables (this review). |

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**Table 2:** Schematic representation of relationships between various kinds of models for parasitic infections, based on relative time scales of population processes.

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between susceptible and infected people or $\beta N w$ for direct transmission between hosts and free-living infective stages are replaced by expressions of the general form $AXY/(1 + \nu Y)$ or $ANP/(1 + \nu N)$, respectively. In the limit when, for example, $\nu Y$ is small, the expression has the familiar form, proportional to $X$ and $Y$. But it can be that $\nu Y$ becomes significant compared to unity, whereupon the transmission term saturates to a value $(AXY)/\nu$ proportional only to $X$. Such saturation effects can be important in diminishing the ability of the parasite to regulate its host population\textsuperscript{14}.

**Ecology of the transmission process.** Further complications can arise from the ecological nature of the individual links in the transmission process.

For infections that are communicated directly, the assumption that the net rate is proportional to the number of susceptibles and to the number of infectives is clearly reasonable for many diseases, and strikingly successful in explaining the mouse pox and mouse pasteurellosis data\textsuperscript{1}. But for sexually transmitted diseases, for example, this is only plausible in a population that is astonishingly promiscuous and sexually active. In a society whose members typically have only a small number, $\eta$, of sexual partners (independent of the absolute population size), the rate at which an infected person propagates the infection is proportional not to the total number of susceptibles, but to $\eta$ times the probability that a given person is a susceptible; that is, $\beta \nu X Y$ is to be replaced\textsuperscript{21} by $\beta \nu XY/N$. Under these very simple assumptions, the condition for maintenance of such diseases is $\beta \eta > (b + \alpha + \nu)$, independent of the population size. In reality, a more careful treatment of the distribution of degrees of sexual activity within the population is needed\textsuperscript{33}, but the fact remains that infections of this sort are relatively easy to maintain in low density populations.

More broadly, biological insights into the relative time scales associated with the various phases of indirect life cycles enable us to discuss the prevalence of infection in the primary host population by retaining equations (8) and (10) for $X$ and $Z$, in Part I of this article, but replacing equation (9) with the more general expression

$$dY/dt = Y[h - (a + b + \nu)]$$  \hspace{1cm} (15)

The transmission term is here denoted by $h$ (Ross' `happenings'\textsuperscript{18}), and the threshold condition for the disease to increase upon introduction at low levels is clearly that $h > (a + b + \nu)$ in the limit $Y \to 0$. For the simple circumstances of the indirect life cycle that led to equation (14) above, this requirement comes down to the threshold criterion\textsuperscript{20,21}

$$NN' > (a + b + \nu)(\alpha' + \beta' + \nu')\beta'$$  \hspace{1cm} (16)

Note that a large population $N'$ of intermediate vectors can enable the disease to persist, even when the primary host population $N$ is small.

However, for malaria and many other infections borne by biting arthropods, the intermediate vector tends to make a fixed number of bites per week, independent of the number of primary hosts available to feed on. Thus the transmission rate from infected arthropods to people (and from infected people back to susceptible arthropods) is proportional to the biting rate $\omega$ times the probability that a given human is susceptible (or infected), and not simply proportional to the number of susceptible (or infected) people. That is, in equations (12) and (13), $\beta$ and $\beta'$ are to be replaced by $\omega/\nu$. The threshold condition (16) is accordingly modified to\textsuperscript{17,18,20}

$$N' > (a + b + \nu)(\alpha' + \beta' + \nu')\omega^2$$  \hspace{1cm} (17)

Note that latency effects have been neglected here, although they can be important in infections with indirect life cycles, and they certainly modify threshold conditions significantly for malaria\textsuperscript{17} and schistosomiasis\textsuperscript{39}. Infections with intermediate vectors of this character are relatively easy to maintain at low population densities of the primary host, provided only that the ratio of intermediate to primary hosts is sufficiently high. Indeed, equation (17) suggests the infection is actually easier to maintain at low host population levels; the mosquito or other intermediate host population $N'$ is, however, typically dependent on the primary host for blood meals or the like, so that things are not as simple as they might seem. (A more general discussion, from which the threshold relations (16) and (17) emerge as limiting cases, has been given by Dietz\textsuperscript{26}).

Finally, note that (apart from the laboratory experiments on mice) in all our models the host population either is regulated to a stable value by the disease, or else it grows exponentially. In practice, other constraints, set by resources, predators or the like, will eventually limit population growth. Such biological realities can be included in all our models, by introducing a logistic constraint (at a `carrying capacity' $K$) in the growth of the disease-free population\textsuperscript{35}. The resulting situation, for both direct and indirect parasite life cycles, is similar to that illustrated in Figs 1e, f and 2b in Part I, with the host population depressed below its disease-free level $K$, provided the parasite-induced host mortality $\alpha$ is not too large\textsuperscript{1}. Too small an $\alpha$ leads to relatively little depression of the host population; too large an $\alpha$ renders the disease unable to persist, and the host population remains at $K$; maximum parasite-induced depression of the host population is attained for intermediate levels of pathogenicity\textsuperscript{40-43}. This broad statement glosses over many intricacies that can arise (R.M.M. and R.M.A., in preparation), particularly with indirect life cycles when the intermediate vector has a constant biting rate (producing threshold conditions such as equation (17) in simpler models), but the gist is true.

### Population parameters and evolutionary trends

Any discussion of the relations among the population parameters that characterize an infectious disease must ultimately take account of the evolutionary pressures on both hosts and parasites. Population dynamics is always confounded by population genetics.

For example, even if we assume no genetic change in the parasite, its action on the host will select for individuals with reduced susceptibility to the disease. For this reason alone, the pathogenicity of the parasite will tend to decrease through evolutionary time. Conspicuous examples are provided by the presence of the sickling gene (and other blood-group phenomena) in regions where malaria is endemic\textsuperscript{37}, and by the history of myxomatosis in rabbit populations in Australia\textsuperscript{44}. An interesting theoretical discussion has been given by Gillespie\textsuperscript{39}.

Selective forces also act strongly on the parasites\textsuperscript{40-44}. As we have seen, the persistence of a disease is facilitated by low pathogenicity and by long duration of infection with intervening formal periods; however, activity to increase the virulence of an infectious disease; increased pathogenicity may often be associated with enhanced rates of production (within the host) of the parasite's transmission stages\textsuperscript{38,42,43}.

The regulatory potential of an infectious disease will, therefore, typically change as time goes by. A parasite may stably regulate its host population during its early association. But,
as selective pressures reduce the average susceptibility of the hosts, such regulatory effects will tend to wane. Eventually, the host population may escape being controlled by the parasitic infection.

Because the generation times of most hosts are several orders of magnitude longer than those of their parasites, it is tempting to conclude that selection acts more rapidly on the parasites. However, the way parasitic infections act within host populations makes it likely that the parasites force the pace of host evolution to keep in step with, or even ahead of, their own evolution.

Among the recondite variety of strategies that parasites have evolved for persistence and transmission, some general trends can be discovered. For example, many parasitic species traverse links in community food webs by virtue of predator-prey associations between primary and intermediate hosts. Such associations, which include biting arthropods feeding on vertebrates, have played an important part in the evolution of complex life cycles. The high transmission efficiency of these links suggest the threshold host populations for maintenance of such parasites will be low (see equations (16) and (17)). Consequently, we expect indirect life cycles to predominate among parasitic infections of hosts that exist at low density.

In contrast, directly transmitted microparasites that require high host densities in order to persist should be more commonly associated with animals that exhibit herd or shoaling behaviour, or breed in large colonies. Empirical evidence in support of these ideas comes from the abundance of directly transmitted viral and bacterial infections within modern human societies42,44, large herds of ungulates45, breeding colonies of sea birds46,47, and the social insects48,49. Those diseases with direct life cycles that do persist within low density host populations should possess distinctive characteristics, such as long-lived infective stages50,51, failure to induce lasting immunity52,53-55, or ability to persist within the host for very long times56.

Another trend to be noted is that highly pathogenic species usually exist, if at all, at low levels of prevalence (see equations (15) and (17) in Part I and equations (7) and (10) in Part II). An example is the digenean parasite Haematolaelchus colaradensis whose primary host is frogs, but which has a transmission pathway involving first snails, and then dragonflies, as intermediate vectors on the way to the next frog. The prevalence among frogs is high, 60-70%, and the parasite is long-lived and has very low pathogenicity; in dragonflies the fluke induces moderate mortality, and has 30-40% prevalence; while in snails it is highly pathogenic but appears to have only about 5-10% prevalence57. These broad patterns, which are often found in helminths with life cycles involving two or three host species, are summarized schematically in Table 3.

Cyclic patterns of disease prevalence

Annual or other cycles in the prevalence of infection are often observed, and can arise in at least three distinct ways.

First, for many short-lived viral and bacterial infections in human populations, there is a propensity for the steady, endemic level of prevalence of infection to be attained by damped oscillations. Particularly if this equilibrium prevalence is low, it is possible for stochastic fluctuations in the number of people infected at the minimum of the cycle to, in effect, keep the cycle 'pumped' and prevent it from damping to equilibrium. This interplay between demographic stochasticity and an inherent propensity to weakly damped oscillations is essentially the mechanism proposed in the classic work of Bartlett19-21,56-59 to account for cyclic patterns in the prevalence of measles and other viral infections in large cities. Gurney and Nisbet60 have proposed a similar mechanism as an explanation for predator-prey cycles.

Second, time dependence in any of the population parameters may, in principle, produce cyclic variations in infection. In particular, seasonal variation in the transmission coefficient is important in setting temporal patterns for many parasitic infections, and may often be central for human viral infections. The mechanisms underlying the seasonality in the transmission rates are poorly understood, but for human viruses the main causes are probably climatic (temperature and humidity) effects influencing survival and dispersal of transmission stages, and seasonal changes in social behaviour66,67 (children returning to school after the long summer vacation). The seasonal cycles characteristic of the prevalence of measles, chicken pox, poliomyelitis and mumps in large cities could arise in this way21,44,65.

Annual periodicity in transmission rates can, moreover, produce complicated nonseasonal cycles in the prevalence of infection. Yorke and co-workers45,46,61, and Dietz47, have cogently argued that such a mechanism is responsible for the regular biennial cycle, alternating between years of high and low incidence, for measles in New York City between 1948 and 1964; in the same city, mumps and chicken pox showed clear annual cycles. The explanation of Yorke et al, is to the contrary of the conventional explanation of these non-seasonal cycles in terms of demographic stochasticity, as described above. Their model is essentially the set of deterministic equations (1)-(3) in Part I, with an assumed constant number of new susceptibles appearing each year, life-long immunity, and with the system enriched by the inclusion of a brief incubation period during which infected hosts are not infective. The basic feature is that the transmission coefficient \(\beta(t)\) varies seasonally with a 1 yr period. Within a narrow window of parameter values, the number of infected people can show biennial peaks (Fig. 2a) similar to those for measles in New York City. This window separates highly transmissible diseases which produce an epidemic with eventual fade-out, from the diseases with low transmission efficiency which give rise to endemic seasonal patterns of infection (Fig. 2b), as usually shown by mumps and chicken pox.

Third, various kinds of nonlinearities in the transmission terms may produce stable limit cycles, whose periods depend on the population parameters and will rarely be seasonal. People familiar with the ease whereby stable limit cycles arise in predator-prey models may be surprised to learn the structure of most host-parasite models is such that stable cycles do not easily occur. However, they can be produced without excessive contrivance. One simple example is to take the basic equations (8)-(10) of part I, and introduce the possibility of saturation in the transmission by replacing \(\beta XY\) by \(\lambda XY/(\Lambda+X)\). Such a modification can arise naturally4,5, in the manner of the analogous expression in equations (5) and (14), if the term is thought of as deriving from the ‘collapsed’ dynamics of a free-living infective stage. This system can now exhibit stable limit cycles for a specific range of parameter values (corresponding to \(\lambda\) neither too small nor too large). One such stable cycle is illustrated in Fig. 2c. In general, however, little is yet agreed about the kinds of biological processes that can generate nonsessional patterns of disease prevalence.

Multiple stable states of disease prevalence

A growing number of empirical and theoretical studies suggest that many natural assemblies of plants and animals can have a multiplicity of alternative stable states68. Once two or more stable states are possible, the actual state the system settles into

<table>
<thead>
<tr>
<th>Host</th>
<th>Pathogenicity of parasite</th>
<th>Prevalence of infection within host population</th>
<th>Expected life span of host (inversely related to time scale of dynamics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final</td>
<td>Low</td>
<td>High</td>
<td>Long</td>
</tr>
<tr>
<td>Second intermediate</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td>First intermediate</td>
<td>High</td>
<td>Low</td>
<td>Short</td>
</tr>
</tbody>
</table>
but sufficiently severe perturbations are liable to precipitate it.

Worms are unlikely to be mated, so that the disease cannot be
of endemic infection (m > G), the other of parasite absence
parasite burden per human host (m*) will be zero if the rate of
many helminth infections with indirect life cycles, such as
primary to intermediate host, or vice versa (mosquitos biting
mary host; nonlinearities associated with the transmission from
infections can generate such multiple states by three principal
landscape. into an alternative state in a different region of the dynamical
intermediate-host prey); parasite pathogenicity dependent on
man for malaria, or predatory primary hosts consuming infected
state, and 'breakpoint' phenomena that arise in simple models for the
transmission dynamics of schistosomiasis, the features are as discussed in the text. 
Transmission threshold and alternative stable states arising in a model for directly transmitted helminth infections, where it is assumed that the pathogenicity of the disease is related to the nutritional state of the host. The graph shows the mean equilibrium burden of parasites per host, m*, as a function of a parameter, T representing transmission efficiency. The infection cannot persist below a threshold value T1; between T1 and T2 there is a unique low level of disease endemicity; between T2 and T3 two stable levels of prevalence may occur, one high and the other low, separated by a breakpoint (the dashed line); above T3 there is again a unique equilibrium level, corresponding to high average parasite burdens per host. The arrows indicate the stable state to which the system will sw from a given initial value.

depends on the initial conditions. The system will tend to
recover its original configuration if subject to small disturbance, but sufficiently severe perturb will liable to transgress the
into an alternative state in a different region of the dynamical landscape.

The nonlinearities in population models for parasitic infections can generate such multiple states by three principal mechanisms: worm pairing for sexual reproduction in the primary host; nonlinearities associated with the transmission from primary to intermediate host, or vice versa (mosquitos biting man for malaria, or predatory primary hosts consuming infected intermediate-host prey); parasite pathogenicity dependent on the nutritional state of the host.

The first and most fully studied of these categories arises for many helminth infections with direct life cycles, such as schistosomes. It serves to exemplify the phenomenon. As portrayed in Fig. 2e, the equilibrium value of the mean parasite burden per human host (m) will be zero if the rate of transmission (T) from snail to man is below the threshold value T1. Above this threshold, two alternative stable states occur, one of endemic infection (m > 0), the other of parasite absence (m = 0). The basic reason is that at low levels of m the female worms are unlikely to be mated, so that the disease cannot be maintained, even though the transmission parameters are such

as to permit its endemicity if introduced at high values of m. The
two stable states (valley bottoms in the dynamical landscape) are separated by a 'breakpoint' (watershed), indicated by the dashed line in Fig. 2e; disturbances severe enough to cross the breakpoint will carry the system from one state to the other.

These threshold and breakpoint concepts are of obvious
importance to epidemiologists concerned with disease eradication.

Of special importance are the effects that can arise from the
now widely recognised fact that the impact of an infection is often related to the nutritional state of the host. Broadly speaking, malnourished hosts have lowered immunological competence, and are less able to withstand the onslaught of infection. The effective pathogenicity of a parasite therefore tends to increase as host density rises to a level where competition for available food becomes severe. Given certain reasonable assumptions about the exact relation between pathogenicity (a) and host density (N), two stable states may occur for a given set of rate parameters. The outcome of such a model, for a directly transmitted helminth infection, is shown in Fig. 2d. Both states reflect stable endemic disease: one

threshold is characterized by high host density and low worm burdens; the other by low host density (severely depressed by the disease) and high average burdens of parasites. As for the schistosome model of Fig. 2e, the two states are separated by a breakpoint or unstable equilibrium.

The discontinuous switch from low to high levels of infection, following a disturbance severe enough to cross the breakpoint, will show up as an apparent 'epidemic' outbreak of disease, typically producing many host deaths. Interestingly, many documented accounts of disease outbreaks are for host populations at high densities, where stress induced by overcrowding or malnutrition is present. It is very likely that such outbreaks are to be explained by the alternative stable states produced by close links between pathogenicity and nutrition or stress, rather than by the commonly accepted hypothesis of enhanced transmission with high density populations.

Parasitic infections with very complex life cycles may possess
more than two stable states, particularly if predator-prey links are involved in the transmission from one host to the next, as is the case for many helminth parasites. There is a desperate paucity of data, from field or laboratory, bearing on these general points.

Conclusion

This two-part article has blended some new theoretical studies and new analysis of existing laboratory data with a review and synthesis of past and present models for the overall transmission dynamics of parasitic infections. We have defined 'parasite' broadly to include viruses, bacteria and protozoans along with the more conventional helminth and arthropod parasites, and we have concentrated attention upon the circumstances under which the infection may significantly alter the growth rate of its host population.

Some of the theoretical conclusions can be pleasingly supported by hard data, while others remain more speculative. On the whole, we should aim to help elevate the study of host-parasite population dynamics to its proper place in ecological thinking; parasites (broadly defined) are probably at least as important as the more usually-studied predators and insect parasitoids in regulating natural populations.

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Radio studies of the double QSO, 0957+561A, B

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The radio source 0957+561 has at least four components. Two coincide with the optical QSOs, which is in accordance with the hypothesis that the QSOs are images of a single object due to a gravitational lens. There are details of spectra and structure which are more difficult to reconcile with the hypothesis.

The pair of QSOs (0957+561A, B) have been shown to have remarkably similar optical characteristics by Walsh, Carswell and Weymann\(^1\) and they suggest that the QSOs may be two images of the same object formed by a gravitational lens. The detailed properties of the radio source are clearly of great interest, and we present here a radio map and other observations discussed in the context of a gravitational lens.

**Observations**

The total flux density of the radio source has been measured at various frequencies summarised in Table 1. The data are consistent with a flux density \(S \propto \nu^{-0.62}\). The two observations at \(\lambda 6\) cm suggest the possibility of variability.