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The regulation of gastrointestinal helminth populations

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SUMMARY

One quarter of the world's human population suffers infection with helminth parasites. The population dynamics of the ten or so species, which cause disease of clinical significance have been well characterized by epidemiological field survey. The parasites are in general highly aggregated between hosts, and their populations seem to be temporally stable and to recover rapidly from perturbation, including interventions designed to alleviate disease.

This paper reviews current understanding of the population regulation of helminth species of medical significance. Both empirical (field and laboratory) and theoretical results are included, and we attempt to interpret the findings in the broader context of the population ecology of free-living species. We begin by considering the evidence for regulation from field data concerning the temporal stability of helminth populations within communities and from the results of perturbation experiments. The detection of regulatory processes is then discussed (with regard to statistical and logistical considerations), and the evidence from both the field and laboratory studies reviewed.

Deterministic models are described to investigate the possible consequences of regulation imposed at different points in the parasite life-cycle. The causes and consequences of parasite aggregation are considered, and a stochastic model used to investigate the impact of different combination of regulatory processes and heterogeneity generating mechanisms.

1. INTRODUCTION

Helminths are very common parasites of humans, infecting a sizeable proportion of the population; *Ascaris*, for instance, is estimated to infect some 1000 million people. The most abundant species are *Ascaris lumbricoides*, the hookworms *Necator americanus* and *Ancylostoma duodenale*, *Trichuris trichiura*, *Enterobius vermicularis* and *Schistosoma* spp., and it is on these that the paper concentrates.

There is a large amount of literature associated with the epidemiology of these species (see, for example, Anderson & May (1985*a*); Bundy & Cooper (1989); Crompton *et al.* (1985); Rollinson & Simpson (1987)). There are, however, noticeable gaps in the available data. These arise mainly from the ethical requirement to treat people where possible, thus making long-term observational studies unacceptable, and the necessity to spend considerable effort persuading subjects to collaborate, thus reducing sample sizes. Experimental studies on humans are, to a large extent, impossible. Consequently we have taken examples from helminths of non-human animals (both laboratory and agricultural), in an attempt to derive conclusions concerning the population dynamics of human infections.

We begin by examining the available evidence for the stability of helminth populations from long-term population studies and perturbation experiments. We discuss the regulatory mechanisms that may be operating in the light of experimental systems that manipulate host nutrition and host immunity and studies of complete parasite transmission systems. The difficulties associated with the detection of density dependence in the field are considered with particular respect to helminth fecundity, size and the host immune response. Finally, we present some preliminary results from a simulation model that examines the interaction between the generation of heterogeneity in helminth burdens between hosts and different density-dependent mechanisms.

2. EVIDENCE FOR POPULATION REGULATION

Evidence for the regulation of helminth populations has come largely from long-term studies of helminth infection without intervention, and from perturbation experiments, in which the population of a helminth parasite is reduced by antihelminthic treatment and the population size followed after the cessation of control.

(*a*) *Long-term population studies*

The persistence of populations for long periods of time is clearly suggestive of regulation. Ethical considerations mean that there have been few long-term studies of human parasite populations without intervention. Such studies often show a remarkably

constant population size over time, both within host populations and within individual hosts (Anderson & May 1985*a*; Anderson 1986). One of the longest runs of data is of the prevalence of *Taenia saginata* in its cattle intermediate host in Kenya. This shows a more variable pattern, the prevalence of heavy infections varying between 0.5% and 19.1% during a 55-year period (Froyd 1965).

Evidence for stability from long-term studies of helminth populations in non-human animals is less conclusive. Although temporal constancy is often observed (Anderson 1979), there are also studies which have recorded large temporal changes in parasite population size. For instance, epizootics of acanthocephalans of many species have been reported (reviewed by Nickol (1985)) and Montgomery & Montgomery (1990) recorded large changes in the intensity of nine helminth species in wood mice *Apodemus sylvaticus* over a five-year period. In each of six study sites at least one helminth species was lost or gained.

(*b*) *Perturbation experiments*

The strongest evidence for the regulation of animal populations comes from perturbation experiments (Murdoch 1970). Parasitologists are thus fortunate that, at least for human helminth infections, a considerable body of data on the effects of perturbation is available (Anderson & May 1985*a*). These data come from studies of the effect of antihelminthic treatment on all the five major gastrointestinal helminth infections of man.

Mathematical modelling of reinfection has revealed several factors that will influence the rate of reinfection (Anderson & Medley 1985).

(1) Reinfection is related to the lifespan of the parasite, with short-lived parasites showing the greatest percentage reinfection.

(2) Percentage reinfection will be greater in children than in adults, since the time over which reinfection occurs will be a proportionately larger fraction of the time children had been exposed to infection before treatment.

(3) Reinfection rate will depend on both the basic reproductive rate of the parasite and on the degree of reduction in work burden achieved by drug treatment (i.e. on the efficacy of the drug and the proportion of the population treated).

(4) Variation in parasite transmission with time will clearly be important. This may result from the provision of increased sanitation at the time of treatment (see, for example, Hill (1926)) or from climatic variation affecting transmission (Wilkins 1989).

Figure 1 shows the results from studies of reinfection with *Ascaris*, hookworm and schistosomes. The choice of study was limited to those that encompassed the whole age range of the population. In all studies treatment was followed by relatively rapid reinfection, and the intensity in some cases approached the pretreatment level after several months or years. Unfortunately, none of the studies was continued for a long enough period to show conclusively that intensity returns to, and is maintained at, the pretreatment level.

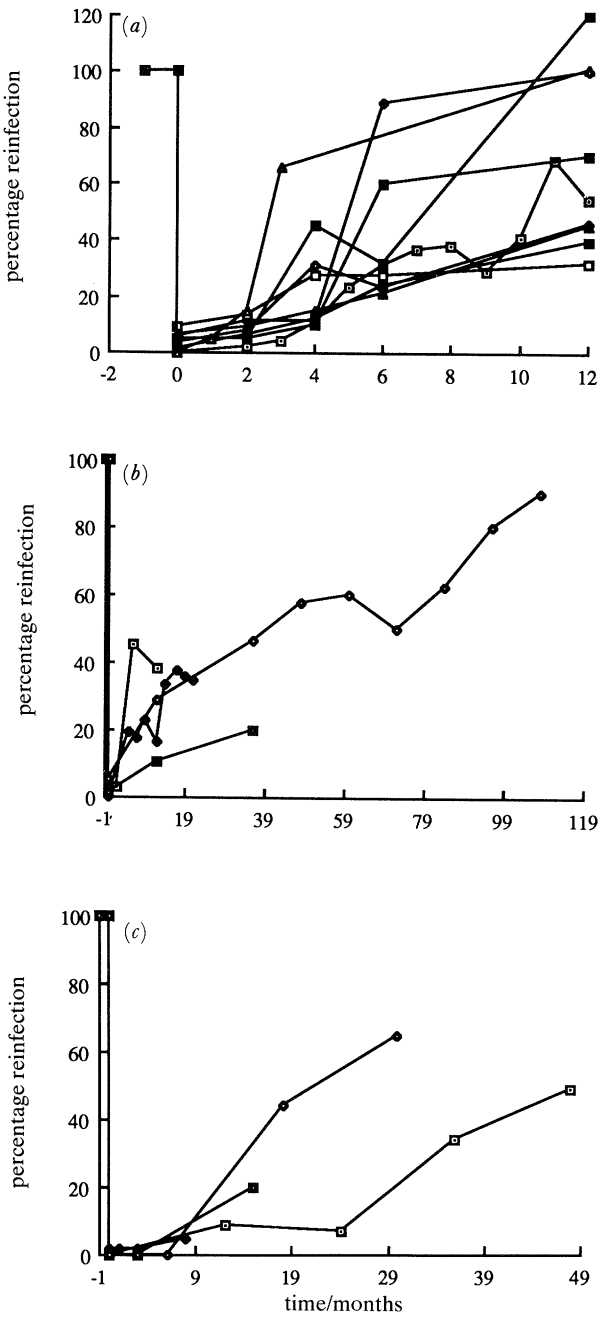

Figure 1. Reinfection after treatment of human helminth infection. Proportion reinfection was assessed as the proportion of the pretreatment faecal egg count (or worm burden, Seo *et al.* (1980)), or as the proportion of the faecal egg count of an untreated control group (Roux *et al.* 1975; Duke & Moore 1976). (*a*) *Ascaris* infection. Data from Arfaa & Ghadirian (1977); Croll *et al.* (1982); Seo *et al.* (1980); Thein-Hlaing *et al.* (1987). (*b*) Hookworm infection. Data from Hill (1926); Sweet (1925); Schad & Anderson (1985); Haswell-Elkins *et al.* (1988). (*c*) Schistosome infection. Data from Roux *et al.* (1975); Duke & Moore (1976); Wilkins *et al.* (1987); Sturrock *et al.* (1987). The first three studies were of *Schistosoma haematobium*, the last of *S. mansoni*.

Repeated measurements of parasite intensity, such as those shown in figure 1, can only be done indirectly using faecal egg counts. These may not always accurately reflect intensity, as parasite fecundity has

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Table 1. *Reinfection with gastrointestinal helminths*

(The initial intensity of infection, the percentage reinfection after a certain number of months and the age range of the host population studied. The estimated lifespan of the parasite (from Anderson & May (1985*a*)) is given in years.)

references	species	initial intensity	percentage reinfection	time (months)	age (years)	lifespan (years)
Haswell-Elkins *et al.* (1988)	Hookworm	2.2	35	11	—	2–4
Bundy *et al.* (1985)	*Trichuris*	114.9	173	7	2–8	1–3
Bundy *et al.* (1987)	*Trichuris*	54.2	44	17	—	—
Holland *et al.* (1989)	*Ascaris*	11	32	6	5–16	1–2
Thein-Hlaing *et al.* (1987)	*Ascaris*	10.7	37	6	—	—
	Ascaris	8.7	76	12	—	—
Elkins *et al.* (1988)	*Ascaris*	9.9	55	11	—	—
Forrester *et al.* (1990)	*Ascaris*	10	120	6	2–10	—
Seo *et al.* (1979)	*Ascaris*	1.2	33	6	—	—
Seo *et al.* (1980)	*Ascaris*	0.6	5	2	—	—
		1.4	45	4	—	—
		1.3	32	6	—	—
		0.8	120	12	—	—
Haswell-Elkins *et al.* (1987)	*Enterobius*	25.7	156	11	—	0.1–0.2

been observed to increase after treatment (Haswell-Elkins *et al.* 1988; Elkins *et al.* 1988). Studies using only faecal egg counts may thus overestimate the amount of reinfection. Accurate measurement of parasite intensity can only be achieved by destructive sampling of the parasite. Details of those studies which incorporate direct worm counts both before and after treatment are given in table 1. Again, rapid reinfection occurred in all studies, but the timescale was generally too short to demonstrate a return to pretreatment levels. The degree of reinfection was clearly related to the lifespan of the parasite, and in two cases reinfection burdens exceeded those pretreatment.

The available evidence is thus consistent with the hypothesis that helminth populations are regulated, and the universal rise in parasite burdens after treatment is strongly suggestive of the relaxation of density-dependent constraints on population growth. The degree of population stability is less obvious, and there is a clear need for more long-term studies of reinfection after chemotherapy.

3. REGULATORY MECHANISMS

Density-dependent constraints are usually considered to act on the parasitic stages of the life cycle, where they may influence parasite establishment, maturation, survival or fecundity. Free-living stages and transmission may also be subject to density-dependent constraints, although these have received little attention.

Several possible causes of density dependence have been identified. The most important of these are likely to be intraspecific competition for resources, such as nutrients or space, and the effects of the host immune response. Additionally, parasite-induced host mortality and host resistance due to parasite-induced pathology may also be density dependent; the former, however, is probably of little importance in human hosts, and the latter is probably only significant in trematode (fluke) infections. Most helminth infections of humans appear to be regulated by either competition or immunity.

The mechanism underlying density dependence may have important epidemiological consequences. The degree of intraspecific competition will depend on current parasite density, which can be approximated by parasite burden. The magnitude of the host immune response, however, will depend not on parasite burden, but on the host's cumulative exposure to infection (strictly speaking on the cumulative exposure weighted according to how long ago exposure occurred). The population dynamics produced by regulation by the host immune response can thus be very different to those due to competition. All forms of density dependence acting within the primary host and related to current worm burden produce only stable dynamics, with one non-zero equilibrium point. When dependence on some measure of cumulative past exposure is introduced (essentially a distributed time delay), oscillatory behaviour may result (Anderson & May 1985*b*).

Many laboratory studies have shown density dependence, typically by examining the effects of parasite density in primary infection. However, the results from primary infections do not allow inferences to be made about the causative mechanisms of density dependence. In a primary infection parasite density will be highly correlated with exposure to the parasite; whatever the generative mechanism, similar patterns will be expected. Disentangling the relative importance of competition or immunity requires experimental protocols that manipulate either the resources available to the parasite or the host's immune response.

(*a*) *Manipulation of nutrient supply*

As endoparasites obtain all their nutrients from the host, their nutrient supply can be readily manipulated by altering the host's diet. This is likely to have a marked and immediate effect on gastrointestinal parasites which obtain nutrients from the intestinal contents, such as cestodes, acanthocephalans and some nematodes. It may have less effect on parasites that feed on host tissues.

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The effects of host diet on density dependence have been best studied on infections of the tapeworm *Hymenolepis diminuta* and the acanthocephalan *Moniliformis moniliformis* in rats. These studies have concentrated on manipulation of the carbohydrate content of the diet, and have shown that the effects of increasing parasite density can be mimicked by the feeding of a carbohydrate-deficient diet (Read 1959; Keymer *et al.* 1983).

Evidence for a role of competition for food in the regulation of nematode and trematode infections is less clear. The feeding of nutrient-deficient diets (such as protein, protein-energy or vitamin A deficient diets) to schistosome infected mice is known to result in decreased worm burden, worm size and worm fecundity, but how this relates to density dependence is not clear. In contrast, many nematode species generally do better in hosts fed protein-deficient diets, presumably as a result of impaired host immunity (Dobson & Bawden 1974; Slater & Keymer 1986).

(*b*) *Manipulation of host immunity*

A large number of studies have shown that there is an immune response to helminths, and that the immune response can act to decrease worm establishment, development, survival and fecundity (reviewed by Wakelin (1986)). The magnitude of the immune response is dependent on the immunising dose, and thus immunity clearly has regulatory potential.

If density dependence is due at least partly to immunity, then its severity should be reduced in immunocompromised hosts, and increased in immunized hosts. *Heligmosomoides polygyrus* in the laboratory mouse is an ideal system for the study of the effects of host immunity, as adult worms immunosuppress the host and the immune response is ineffective in primary infection. In many strains of mice there appear to be no density-dependent constraints during primary infection, and there may in fact be inverse density dependence: the survival of worms is prolonged in heavy infections, as the degree of immunosuppression increases with parasite burden (Robinson *et al.* 1989). Similarly, Slater & Keymer (1986) found no density-dependent constraints on parasite population growth during repeated infection of protein-malnourished hosts which lack a functional immune response. In contrast, populations in well-nourished hosts were strongly regulated by the host immune response.

(*c*) *Studies of complete systems*

Density dependence during a primary infection in the laboratory may have little relevance to the population dynamics of the parasite in the field. Yet it is important to identify the underlying mechanisms in the field, and the stages in the parasite life cycle they act on. One approach to this problem is to study population dynamics during repeated infection. If the dynamics of different parasitic life-cycle stages are known, then mathematical modelling may allow an assessment of the importance of regulatory processes, and the mechanism behind them. This approach has been successfully used to study two cattle nematodes, *Ostertagia ostertagi* (Grenfell *et al.* 1987) and *Haemonchus contortus* (Smith 1988).

Table 2. *Empirical descriptions of density-dependent constraints on the parasitic stages of* Ostertagia ostertagi *and* Haemonchus contortus — *the factors important in influencing parasite establishment, arrestment, mortality and fecundity during repeated infections*

(E, cumulative exposure to infective stages; t, time since start of infection; N, parasite burden (density). From Grenfell *et al.* (1987); Smith *et al.* (1987) and Smith (1988))

	O. ostertagi	*H. contortus*
establishment	e^{-at}	$\frac{e^{(a-bt)}}{1+e^{(a-bt)}}$
arrestment	none	$a+bt$
mortality	$a+bE$	$a+bE$
fecundity	e^{-aNt}	—

The results of these studies are shown in table 2. The mechanisms behind the regulatory processes can be inferred from their dependence on parasite density (implying competition) or exposure (implying immunity). Mortality and fecundity appear to be exposure-dependent, suggesting that the host immune response is of overriding importance. Surprisingly, establishment and arrestment appear to be independent of both current density and exposure, although they are time dependent.

Models based on laboratory data have also been produced for *Taenia hydatigena* and *Echinococcus granulosus* infection. The only regulatory process identified in *E. granulosus* infections is the immune response in the ovine intermediate host, and there appears to be no density-dependence in the canine final host (Gemmell *et al.* 1986). *T. hydatigena* can be regulated in the final host by density-dependent constraints on growth and fecundity, but in the field immunity in the intermediate host apparently keeps worm burdens below the level at which these constraints start to operate (Gemmell *et al.* 1987). Neither species affects the mortality of either the final or intermediate host. Models incorporating intermediate host immunity as the only regulatory process give an accurate representation of population dynamics in the field, and the consequences of intervention (Roberts *et al.* 1986, 1987).

4. THE DETECTION OF REGULATORY PROCESSES IN THE FIELD

The mechanism responsible for regulation will have important consequences for the detection of density dependence in the field. Since cumulative exposure to helminths has not been measured in the field, the detection of regulatory processes has relied on the demonstration of dependence on current parasite density. This will allow the detection of regulation caused by intraspecific competition. However, the results of laboratory experiments discussed above

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suggest that the host immune response may be the most important regulatory mechanism, particularly for nematode populations. Detection of regulation by host immunity will only be possible if there is a correlation between current parasite density and exposure.

The relation between density and exposure is likely to be complex, and to depend on such factors as overall transmission rates and host age. A host with a low worm burden may either have been exposed to few worms (and have no immunity) or have developed an effective immune response to past exposure. Only in very young hosts, which can be considered as experiencing a primary infection, are density and exposure likely to be closely related. An additional complicating factor is the likelihood that there will be genetic heterogeneity among hosts in their ability to mount an effective immune response (reviewed by Wakelin (1988)). In this case, the host's immune response may not be related to exposure in a consistent manner. High exposure will lead to high worm burdens and yet little immunity in low responder hosts, but low worm burdens and high immunity in high responders. There may thus be a negative correlation between current density and host immunity. If parasite fecundity, survival or size is related to immunity, a positive relation between these factors and worm burden would then be expected (Keymer & Slater 1987). Such a positive relation between fecundity and worm burden has been demonstrated in a captive population of wood mice exposed to natural infection with *H. polygyrus* (Quinnell 1990).

(*a*) *Density-dependent fecundity*

The detection of density-dependent processes operating on free-living organisms comes mainly from the analysis of life-table data (reviewed by Sinclair (1989)). The collection of life-table data requires assessments of the numbers of various different life-cycle stages at various time points. For helminth species the only stages of the life cycle that can be quantified are adults (and then only at a single time point) and the total production of eggs or larvae from a single host. Life-table analysis is thus restricted to examining the effect of adult parasite density on parasite fecundity.

A negative correlation between average fecundity and worm burden has been reported for all the major helminth parasites of humans (Anderson & May 1985*a*). However, the variables in such an analysis are not independent, and errors in the measurement of worm burden may bias the data towards a negative correlation. In the field such errors are likely to be large (Anderson & Schad 1985), and Monte Carlo simulations show that artefactual density dependence can be produced (R. J. Quinnell & G. F. Medley, unpublished data).

Problems such as these in the detection of density-dependence in field data can be minimised by the use of regression analysis (Varley & Gradwell 1960; Eberhardt 1970). In the present case, the regression should be that of total egg production on worm burden, which are measured independently. If estimates of the errors in the two variables can be made, the structural relations model will give a maximum likelihood estimate of the slope of the regression line (Sprent 1966; Rayner 1985). Error variances have recently been estimated from a study of human hookworm infection (Pritchard *et al.* 1990). The structural relations model provided no evidence for density-dependent fecundity, despite a significant negative correlation between average fecundity and worm burden (table 3) Analysis of a further five data sets did not produce firm evidence for density dependence, although this analysis was hampered by the lack of estimates of error variances from these studies.

Table 3. *The analysis of density-dependence data*

(Data on human hookworm fecundity (eggs/g faeces) from Karkar I., Papua New Guinea, were analysed (*a*) by correlation between mean fecundity and hookworm burden and (*b*) by regression of total egg production on hookworm burden. All data were log(x) transformed before analysis, and only egg- and worm-positive data were included.)

(*a*) Analysis of mean fecundity data. Pearson's product-moment correlation coefficient (r) for the relationship between mean fecundity and hookworm burden (either females only or total).

	n	r	p
females	93	−0.309	0.0026
total	93	−0.299	0.0036

(*b*) Regression analysis. The slope (b) and 95% confidence limits of the regression line between total egg production and hookworm burden, estimated from the structural relations model with an error variance ratio of 3.05.

	n	b	95% c.l.
females	93	0.953	0.628–1.30
total	93	0.828	0.526–1.14

An alternative approach to the detection of density-dependent fecundity is to use an independent measure of worm fecundity, such as the uterine egg content of female worms. This approach has been used in experimental studies of helminth infection (see, for example, Coadwell & Ward (1982); Shaw & Moss (1989)). Its use in the field has been limited to a single study of hookworm infection, when there was no relation between uterine egg count and parasite density (R. J. Quinnell *et al.* unpublished data).

The available data thus do not provide any firm evidence that fecundity is dependent on current parasite density. It is possible that further studies involving estimates of error variances will allow the detection of a significant relation. However, variation between hosts and between parasites, coupled with the measurement errors discussed above, is likely to make detection difficult (Medley 1989). Either way, the possibility that the fecundity of human helminths in the field is dependent not on current parasite density, but on previous exposure to the parasite, should not be ignored. It is also possible that regulatory processes

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may not act on fecundity, but rather on other stages of the parasite life cycle.

(*b*) *Parasite size*

The relation between worm burden and worm size or mass in the field is simple to examine. Although density-dependent constraints on parasite size need not affect population dynamics, they are likely to be associated with effects on parasite development rate, mortality or fecundity. Several studies have investigated the relation between worm size and worm burden in humans (*Ascaris* (Mello 1974; Cho 1977; Martin *et al.* 1983; Elkins & Haswell-Elkins 1989); *Necator* (R. J. Quinnell *et al.* unpublished data); *Trichuris* (Burrows 1950)). In none of these studies was there a significant relation.

(*c*) *The detection of host immunity*

In view of the importance of host immunity in laboratory infections, it may not be surprising that direct effects of parasite density are not detectable in the field. Attempts to detect immunity in the field have taken three forms. Epidemiological evidence for immunity can be obtained from studies of reinfection rates, providing some estimate of current exposure is made. This has provided strong epidemiological evidence for the role of immunity in schistosome infections (reviewed by Hagan 1987; Butterworth *et al.* 1988*a*), as has a comparison of age-intensity curves from different areas (Anderson 1987). Evidence for immunity to other parasite species is weak and equivocal (reviewed by Anderson 1986; Behnke 1987; Bundy 1988).

Direct immunological correlates of infection or resistance to reinfection have been sought in studies of schistosomes (see above reviews) and hookworm (Pritchard *et al.* 1990). Such studies have mostly failed to show a clearly protective immune response; immunological parameters generally reflect, rather than determine, worm burdens. The complexity of the antibody response to helminth infection, which may include protective, non-protective and blocking antibodies to a wide range of antigens, makes the detection of protective responses difficult. Increasing knowledge of anti-schistosome responses has recently led to the identification of possibly protective anti-schistomulum IgG antibodies (Butterworth *et al.* 1988*b*).

Finally, it is possible, at least for non-human animals, to obtain an empirical measure of host resistance by challenging animals taken from the field. This technique has been used to quantify resistance to reinfection with *Heligmosomoides polygyrus* after either natural infection (Slater 1988) or trickle infection (Keymer *et al.* 1990). Further experiments on the same parasite in wood mice have shown a negative correlation between resistance to reinfection and the worm burden of naturally infected mice, indicating a role for the immune response in determining parasite burdens in a semi-natural situation.

5. AGGREGATION OF PARASITES WITHIN HOSTS

Heterogeneity in worm burdens within human hosts is ubiquitous. As noted previously, any process that depends on the degree of aggregation (as all density-dependent processes will) implies that consideration must be given to the distribution pattern of worms among hosts. This distribution must be viewed as a dynamic as opposed to a static entity, created by a plethora of factors derived from hosts, environment and parasites. Chemotherapy will inevitably alter the distribution. We examine the interaction between heterogeneity and different density-dependent processes by using a simulation model in which the distribution of worms is created rather than assumed to be of some particular form.

A recent study (Guyatt *et al.* 1990) has shown that the aggregation pattern of *Ascaris* in different communities can be described by using the negative binomial distribution with the degree of aggregation decreasing with increasing mean worm burden. The fact that there is a consistent pattern of heterogeneity in different communities leads to the tentative hypothesis that the generative factors are to be found in the biological association between parasite and host and that they are independent of specific environmental factors.

(*a*) *Consequences of heterogeneity*

One immediate effect of heterogeneity is that clinical disease, which is thought to be positively associated with worm burden, is limited to a small proportion of the human population. By using an estimate of the distribution of the worm population throughout the host population, H. Guyatt & D. A. P. Bundy (unpublished data) suggest that this empirical relation can be used to rank communities according to the level of disease caused by *Ascaris* on the basis of prevalence data alone.

More difficult to study is the effect that heterogeneity has on the worm population itself. Most worms live in environments populated with other worms of the same species. The population genetic consequences of aggregation have not been considered in any detail, although Anderson *et al.* (1989) show that it may have a significant effect on the evolution of resistance against chemotherapy. Depending on the methods of infection, it is possible that there is a significant degree of genetic relatedness between worms within an individual host. This aspect has not been considered to our knowledge.

(*b*) *The effect of heterogeneity generation on dynamics*

The details and some results of the simulation model are available elsewhere (Anderson & Medley 1985; Medley 1988, 1989). One of the important results is that if differences in exposure to infective stages is assumed to generate the aggregation observed in adult parasites, then the exact mechanism can significantly alter the dynamics of the parasite population in the

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Table 4. *A brief summary of the assumptions associated with the simulation model discussed in the text*

(Four parasite developmental stages are assumed: immature and mature (within host), free-living uninfective stage and free-living infective stage. The free-living stages are modelled deterministically, and the remaining rates are modelled stochastically using the Monte Carlo technique. The processes are summarized below, where $M_{(i,t)}$ is the number of mature worms in individual host i at time t.)

process	assumption
mature worm death	constant mean rate with 1 year life-expectancy
immature worm death	constant mean rate with 1 year life-expectancy
maturation	density-independent:
	constant mean rate with 6 week average maturation time.
	density-dependent:
	mean rate given by $\sigma \exp\{-a.M(i,t)\}$, where σ is the pristine maturation rate (= 1–6 weeks) and a is a parameter chosen to give the required mean worm burden
fecundity	density-independent:
	constant mean rate with 5 799 500 eggs per week
	density-dependent:
	mean rate given by $\lambda \exp\{-\gamma M(i,t)\}$ where λ is the pristine fecundity rate and γ is a parameter
transmission	
transmission is divided into two processes: contact with and pick-up of infective stages.	
The contact rate is calculated as $\beta.I(t).s_i$, where $I(t)$ is the number of infective stages at time t and β is a transmission coefficient	
susceptibility:	the s_i are random numbers drawn from a gamma distribution with mean unity, and a single worm is picked up on each contact
environmental:	the s_i are all unity, and the number of worms establishing is drawn from a logarithmic distribution with mean unity
host population	constant at 250 hosts
free-living uninfective death	constant mean rate with mean life expectancy 8 weeks
free-living uninfective maturation	constant mean rate with mean time to maturation 3 weeks
free-living infective death	constant mean rate with mean life expectancy 8 weeks

face of perturbation (= chemotherapy). We do not repeat a description of the structure of the simulations here, but include a compendium of relevant biological assumptions shown in table 4. The results presented here are by no means exhaustive, but are intended to make a few salient points regarding patterns that may arise, and data that may provide clues to population dynamic mechanisms.

The generation of heterogeneity can have two causes: differences in exposure to infective stages, and differences in parasite population parameters within different hosts. The former mechanism encapsulates a spectrum, from which we take two illustrative examples. The first heterogeneity generating hypothesis, termed susceptibility, assumes that the immigration rate varies systematically between hosts. Each host has a factor designated at birth and constant thereafter which determines that host's relative resistance/susceptibility to infection compared with the remainder of the population. The second heterogeneity-generating hypothesis, termed environmental, assumes that the immigration rate does not differ systematically between hosts. Each host will experience the same average immigration rate over time, but at any point the values between hosts will vary randomly. Essentially, noise is added to immigration.

The alternative possibility (termed host variation) is that heterogeneity is generated by differences between hosts in their ability to mount effective, density-dependent, immunological/pathological responses to immature parasites. The average rate of maturation, σ, is modified by the factor $\exp\{-s_i M(i,t)\}$, where $M(i,t)$ is the number of mature worms in individual i and time t, and s_i is a factor peculiar to individual host i drawn from a log-normal distribution. In this case we assume that there is no heterogeneity (other than that arising from chance) in host exposure to infectives. Note also that we assume an effect of the current worm burden, not some measure of accumulated past exposure.

We combine these heterogeneity-generating mechanisms with two choices for the site of density dependence: fecundity and maturation. Maturation is defined here as the transition from one stage of development to the next, and not necessarily confined to the development of sexual maturity. For example, the major density-dependent effects may occur during some phase of migration through the host tissues. Only two parasite stages are considered: immature and mature. Thus, we have five different models: susceptibility plus fecundity or maturation density dependence, environmental plus fecundity or maturation density dependence and host variation in maturation density dependence (the combination of host variation on density-dependent fecundity will result in population regulation, but not heterogeneity.

(*c*) *Results*

The results are summarized with respect to two aspects: the equilibrium situation which may be

detected through a single, horizontal survey of an infected community, and the response of the parasite population to a single round of chemotherapy (perturbation).

At equilibrium, the two features of interest are the relative numbers of immature and mature worms within individual hosts, and their frequency distribution between hosts. When density-dependent maturation is operating equally for all hosts regardless of which hypothesis is generating heterogeneity (susceptibility or environment), the number of immature worms is greater in relation to the number of mature worms than when maturation is constant (figure 2). When maturation occurs at a constant rate, the ratio of mature to immature worms within individual hosts is approximated by the ratio of the maturation rate to the adult worm death rate, and will be typically less than unity. If the maturation rate decreases with increasing mature worm burden then not only will the ratio be much higher, but will increase with increasing mature worm burdens. If there is significant variation in the abilities of hosts to delay maturation, then a reverse pattern is seen: those hosts with few mature worms have few because they prevent maturation, and consequently have higher immature burdens and vice versa.

The introduction of density-dependent maturation tends to decrease the frequency of hosts with very high burdens, and decrease the numbers of hosts with zero and low worm burdens. When exposure to infective stages is high, a large number of immature worms accumulates in response to the high number of mature worms. As these mature worms die, they are replaced from the pool of immatures, consequently generating a mode of observations close to the mean. This has not been the typical observation from the field, and shows that either some modification of survival of immature or mature worms is likely to complement or replace density dependence within the life cycle. During the exposure to infective stages is more extreme than assumed here.

Figure 3 shows differences in the recovery of the parasite population with different assumptions following a single round of chemotherapy. After an initial period of five years, 80 % of the human community was chosen at random, and all the worms (mature and immature) removed from them. Density-dependent maturation induces faster recovery of the parasite population than when density-dependent fecundity is the limiting process. This is because of the site of density dependence within the life cycle. During the first 1–2 years following chemotherapy, those individual hosts that will develop large worm burdens can do so without density-dependence acting. Also, when large mature burdens are developed in some hosts the rate of recovery in the remaining hosts is unaltered, unlike the effect of fecundity. Thus the slower rate of recovery for the case of susceptibility generated heterogeneity with density-dependence fecundity.

The reacquisition of heterogeneity causes the two slowest population recovery rates, host variation and environmentally generated heterogeneity with density-dependent fecundity. Environmental heterogeneity

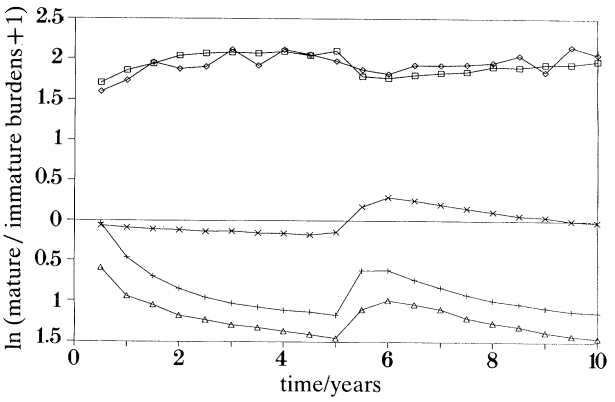

Figure 2. The ratio of mature : immature worms in response to a single round of random, mass chemotherapy. Note the logarithmic scale. The chemotherapy was applied at year five, after five years of equilibration, and killing all worms (immature and mature) in 80 % of hosts chosen at random. Each line is the ratio of the mean mature to mean immature burdens of 10 simulations of 250 hosts each. The lines are: (*a*) (□), susceptibility generated heterogeneity, density-dependent fecundity; (*b*) (+), susceptibility generated heterogeneity, density-dependent maturation; (*c*) (◇), environmental generated heterogeneity, density-dependent fecundity: (*d*) (△), environmental generated heterogeneity, density-dependent maturation, and (*e*) (×), heterogeneity generated by variation in maturation rates.

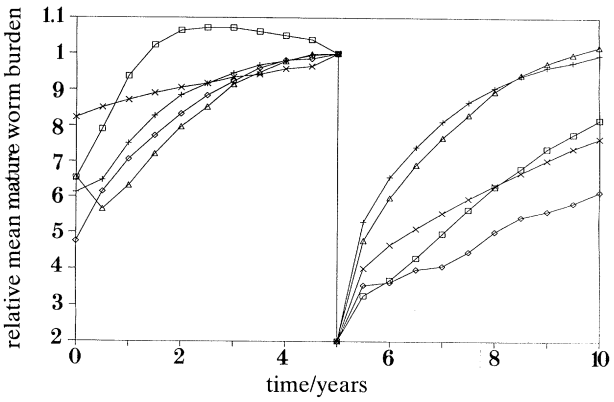

Figure 3. The rate of recovery of the mature parasite population following a single round of random mass chemotherapy. The chemotherapy regime applied was as shown in figure 2. Each line is the mean of 10 simulations of 250 hosts each, and have been adjusted by a factor such that the mature burden at chemotherapy is unity. The lines are: (*a*) (□), susceptibility generated heterogeneity, density-dependent fecundity; (*b*) (+), susceptibility generated heterogeneity, density-dependent maturation; (*c*) (◇), environmental generated heterogeneity, density-dependent fecundity; (*d*) (△), environmental generated heterogeneity, density-dependent maturation, and (*e*) (×), heterogeneity generated by variation in maturation rates.

immediately reintroduces the same degree of overdispersion (compared with susceptibility generated heterogeneity in which those hosts with large burdens must reacquire them over time). Likewise, in the host variation case, the heterogeneity is generated immediately by different maturation rates between hosts. Consequently, density-dependent restraint is reintroduced more quickly.

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Figure 2 shows the response of the ratio of mature to immature worm burdens through the same chemotherapy régime as previously applied. Those cases where density-dependent maturation is operating show an increase in the ratio following chemotherapy, as opposed to a decrease when parasite development is constant. This is again because of the large number of immature worms available for maturation when relatively small mature burdens are removed.

Increasing our knowledge of the 'demography' of the parasite within the definitive host will greatly increase our knowledge of the population dynamics of the parasite. Some progress has been made in this direction by looking at the size distribution of parasites and the changes induced by chemotherapy (Elkins & Haswell-Elkins 1989). These data show a dramatic shift in weight distribution of *Ascaris* in children after chemotherapy. At treatment, smaller worms outnumber larger worms, although the reverse is true following nine months reinfection. Interestingly, this change does not occur in adults. This may suggest that some form of density-dependent maturation or development is occurring in children but not adults.

By considering the developmental stages within the definitive host, both in cross-sectional and perturbation surveys, some conclusions may be drawn regarding the population dynamics of the parasites. One remaining problem is the definition of immature worms in this context. It is likely that they constitute the tissue migratory stages rather than sexually immature stages within the gut lumen. Consequently, indirect methods of investigation will be required in human hosts, although direct investigations on animal models may be useful. It is also possible that developmental stages may be distinguished by the molecular markers that they exhibit. What is required is a molecular or immunological score of intensity of infection that is specific to a stage in the parasite's development and which is quantitative enough to distinguish relatively small changes in worm burden.

6. CONCLUSIONS

This brief review of the evidence suggests two main conclusions. First, there is strong evidence that many helminth populations are subject to regulation, especially in human hosts (Anderson & May 1985*a*). Even so, there is a need for more field studies: for instance, there is evidence for the stability of only one acanthocephalan species (Kennedy 1985). Secondly, evidence for the importance of particular regulatory mechanisms or processes is much less conclusive.

An important difference between the ecology of parasites and that of free-living organisms is the influence of host defences, particularly the immune response. If the host immune response is important, there may be very different ecological and evolutionary constraints on parasitic helminths than on their free-living counterparts. Laboratory studies suggest that immunity can be of overriding importance, yet our knowledge of the importance of immunity in the field is so sketchy that we cannot rule out the possibility that it may be largely irrelevant (Wakelin 1984). This lack of knowledge stems partly from the difficulties in assessing immunity, particularly in human hosts, but this is because of the relatively little attention that has been paid to the identification of the regulatory processes affecting helminth populations. Although there have been a large number of laboratory studies, very few studies have attempted to combine field and laboratory work.

Knowledge of the mechanisms regulating helminth populations is also of considerable applied importance, both for the design of chemotherapy control programmes (Anderson & May 1985*b*) and for the development of vaccines. Combined with simple economic arguments, our current, limited understanding of helminth population dynamics is enough to aid in the design of control programmes. However, it is important to continue to collect appropriate data, both to satisfy academic curiosity and to improve health-care policies.

Discussion

P. J. Grubb (*Botany School, Cambridge University, U.K.*). Do I understand that the failure to detect density dependence in the fecundity of the intestinal worms in wild populations results from the great variation in background conditions, e.g. densities of competitors, or is it overwhelmingly a result of variable control by the immune response system?

A. E. Keymer. The detection of density-dependent fecundity will always be hampered by unavoidable errors in the assessment of both fecundity and density, and by variability in both host (genetics, nutrition, presence of other parasite species, etc.) and parasite populations. Unfortunately, it is not possible to decide between the two possibilities outlined by Dr Grubb: that the failure to detect density-dependence is only because of these effects, or that the effect of the host immune response means that there really is no relationship between fecundity and current parasite density.

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