Parasitic Infections as Regulators of Animal Populations

The dynamic relationship between parasites and their host populations offers clues to the etiology and control of infectious disease

Robert M. May

Many field, laboratory, and theoretical studies have focused on the possibility that competition or prey-predator interactions may regulate animal numbers and influence the geographical distribution of species. On the other hand, the growing body of research on the transmission and maintenance of infectious diseases usually assumes that the host population is constant, not dynamically engaged with the disease. This article outlines recent work which weaves these two strands together, with the aim of understanding how parasitic infections may act as regulatory agents in natural populations of animals.

In what follows, the term *parasite* is used broadly to include viruses, bacteria, protozoans, and fungi along with the helminths and arthropods more conventionally defined as parasites. I begin with a number of anecdotes about the dynamical effects of parasites on particular host populations. Some useful concepts (including the intrinsic reproductive rate of the parasite and the effects of host density) are next introduced, and applied in an analytic discussion of a classic series of laboratory experiments in which mice populations were regulated by viral or bacterial infections. The discussion then broadens to consider general patterns in the regulation of natural populations by parasitic infections, and I go on to apply some of these ideas to that most fascinating of animal populations, *Homo sapiens*. The article concludes by touching very briefly on evolutionary aspects of host-parasite associations.

There is abundant evidence that parasites, in the broad sense defined above, cause many deaths in natural populations. Thus Delyamure's survey shows that helminths contribute significantly to the mortality rate in many populations of pinnipeds and cetaceans (*1*); one particularly careful study, for example, suggests that 11 to 14% of deaths among spotted dolphins (*Stenella* spp.) are caused by nematode infections in the brain (*2*). Lanciani has demonstrated that an ectoparasitic mite influences the population dynamics of the aquatic insect *Hydrometra myrae* (*3*). Lloyd and Dybas have suggested that the ultimate determinant of the population densities of the spectacular 13- and 17-year periodical cicadas is a fungal infection, *Massospora cicadina* (*4*). Many studies have shown that infectious diseases are an important, and possibly the predominant, mortality factor in bird populations (*5*).

Parasites can also affect the outcome of competition among species. This was shown in Park's (*6*) classic laboratory experiments on competition between two species of flour beetles: when the sporozoan parasite *Adelina* was present it dramatically reduced the population density of *Tribolium castenetum*, and in some situations reversed the outcome of its competition with *T. confusum*. The simian malarial parasite, *Plasmodium knowlesi*, is highly pathogenic for the rhesus monkey *Macaca mulatta*, but produces a chronic and much less lethal infection in *M. fascicularis*; *M. mulatta* is distributed widely throughout central, northern, and western India, where the malaria mosquito vector, *Anopheles leucosphyrus*, is absent, but is replaced by *M. fascicularis* in eastern India and parts of Bangladesh where *A. leucosphyrus* is present (*7*). On a grand scale, it seems that the geographical distribution of most artiodactyl species in East Africa today is determined largely by a pandemic of the rinderpest virus that occurred toward the end of the nineteenth century.

In many cases, different species of parasites combine to kill the host. Thus among bighorn sheep in North America the main cause of death is probably infection by the lungworms *Prostostronglylus stilesi* and *P. rushi*, which then predispose the hosts to pathogens causing pneumonia (*8*). More generally, it may be that the interplay between parasitic infections and the nutritional state of the host contributes importantly to the density-dependent regulation of natural populations.

Despite these illustrations of the devastating effects that diseases can have on natural populations, it is hard to assess the extent to which diseases are the primary regulators of such populations, as opposed to acting as occasional or incidental sources of mortality. For example, among certain species of wildfowl in North America some 80 to 90% of the individuals not shot by hunters die of diseases each year, yet it remains arguable that the essential factor regulating population density is the availability of breeding sites (*9*). In a study with implications for many insect populations, both temperate and tropical, Wolda and Foster (*10*) have documented outbreaks of the larvae of a tropical moth, *Zunacetha annulata*, which cause severe defoliation and are ended by a fungal infection; the key determinants of the overall population dynamics of this moth, however, remain

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enigmatic. Delyamure (*1*) sums it up in his lament that "unfortunately, so far the influence of helminths on the population dynamics of pinnipeds and cetaceans has not been investigated at all" (p. 517), despite its likely importance.

In a recent review of the empirical evidence, Holmes (*9*) suggests that invertebrate populations and vertebrate populations in disturbed situations may more typically be regulated by parasitic infections than are natural populations of vertebrates. I now proceed to sketch an analytic framework within which these questions and suggestions may be pursued.

Microparasites and macroparasites

By classifying parasites according to their population biology rather than their conventional taxonomy, we can make a rough but useful distinction between microparasites and macroparasites (*11*).

Broadly speaking, microparasites are those having direct reproduction, usually at very high rates, within the host. As exemplified by most viral and bacterial, and many protozoan, infections, microparasites tend to be small in size and to have short generation times. Although there are many exceptions, the duration of infection is typically short relative to the average life-span of the host, and hosts that recover usually possess immunity against reinfection, often for life. Microparasitic infections are thus characteristically of a transient nature.

Macroparasites are broadly those having no direct reproduction within the host. This category embraces essentially all parasitic helminths and arthropods, which typically are larger and have much longer generation times than microparasites. When an immune response is elicited, it usually depends on the number of parasites present in the host, and tends to be of relatively short duration. Thus macroparasitic infections are typically of a chronic or persistent nature, with hosts being continually reinfected.

For microparasites, it generally makes sense to divide the host population into three distinct classes: susceptible; infected; and recovered and immune (*12*). Such a "compartmental" model for the dynamics of a host-microparasite system is shown schematically in Figure 1, and will be discussed further below. For macroparasites, on the other hand, the various factors characterizing the interaction—egg output per parasite, pathogenic effects upon the host, evocation of an immune response in the host, parasite death rates, and so on—all tend to depend on the number of parasites present in a given host (*13, 14*).

It follows that, for many macroparasites, a medically significant distinction can be made between infection (harboring one or more parasites) and disease (harboring a parasite burden large enough to cause illness). In other words, for an archetypal microparasitic infection such as smallpox it is reasonable to assume that a given individual either does or does not "have smallpox"; but for a macroparasite such as hookworm or schistosomiasis there is a real difference between being infected with one or two worms and carrying a worm load large enough to cause disease.

Reproductive rates and thresholds

For a discussion of the overall population biology of any organism, a central concept is its intrinsic reproductive rate, R_0. For parasites, R_0 essentially measures the number of offspring that can be produced; R_0 depends both on the basic biology of the parasite and on ecological, environmental, and behavioral factors that can influence transmission rates (*15–18*).

More precisely, for microparasites R_0 is defined as the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible. For macroparasites, R_0 is the average number of female offspring produced by a mature female parasite over her lifetime that themselves achieve reproductive maturity in the absence of density-dependent constraints.

In either case, it is clear that R_0 must exceed unity for a parasite to be capable of establishing itself within a host population. In simple situations, it may often be assumed that R_0 is directly proportional to the total number of hosts that are candidates for infection, whence we can write

$$R_0 = N/N_T \qquad (1)$$

Here N is the host population size, and the proportionality constant (which subsumes all manner of biological and environmental aspects of the transmission process) has been written as N_T^{-1}. The condition $R_0 > 1$ for establishment of the infection thus translates into the requirement that the host population, N, exceed a given threshold magnitude, N_T (*12*).

More generally, R_0 may be some nonlinear function of the host population, $R_0 = f(N)$. The criterion $R_0 > 1$,

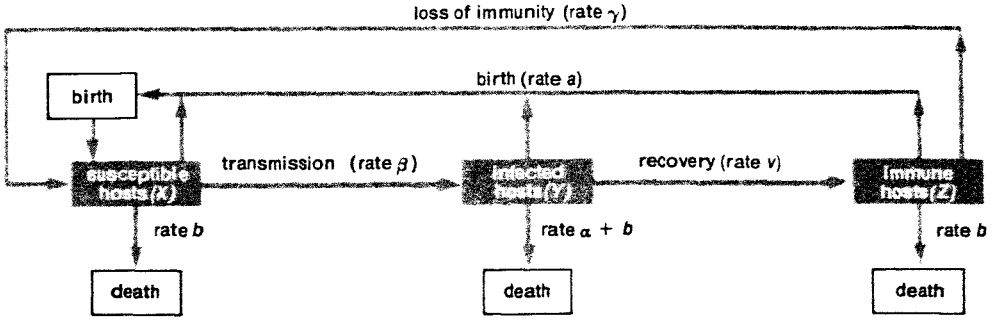


Figure 1. In this schematic representation of the dynamics of a host-parasite association, the host population is divided into susceptible (*X*), infected (*Y*), and immune (*Z*) classes. Susceptible individuals are gained through birth or through loss of immunity at rates *a* and γ, respectively, and are lost through natural mortality at rate *b* or by acquiring infection. Infected individuals are lost by disease-induced mortality, natural mortality, and recovery into the immune class at rates α, *b*, and ν, respectively.

however, will still usually lead to some threshold condition, $N > N_T$. An important class of exceptions is sexually transmitted infections. Here R_o depends on the average rate at which new sexual partners are acquired, which usually has no direct dependence on N; doubling the population size does not affect sexual habits, except indirectly through possible social changes caused by greater crowding. Sexually transmitted parasites, which produce long-lasting infections and do not induce acquired immunity in recovered hosts, can be admirably adapted to persist in low-density populations of promiscuous hosts.

Direct assessment of the threshold density, N_T, is usually difficult. Some useful generalizations can, however, be made. Many microparasitic infections, such as smallpox and measles in man, are of very short duration and have relatively low transmission efficiencies; that is, the transmission stages may be short-lived in the external environment, and fairly direct contact may be needed to acquire infection. In this event, a large population of candidate hosts will be required before R_o can exceed unity, and thus the threshold density for the host population, N_T, will be large. Specifically, it has been estimated that the threshold population for maintaining measles in human communities is around 300,000 individuals or more (*19, 20*). Conversely, the reproductive life-span of many macroparasites within a host is often an appreciable fraction of the host's life, and transmission pathways are often quite efficient, involving intermediate vector hosts or long-lived transmission stages. Threshold host densities for the maintenance of macroparasite populations can thus be small.

In short, directly transmitted microparasites typically require high host densities in order to persist, and should more commonly be associated with animals that exhibit herd or schooling behavior or that breed in large colonies. A certain amount of anecdotal support for these ideas comes from the observed abundance of such infections within modern human societies, large herds of ungulates, breeding colonies of seabirds, and communities of social insects (*11*). But there is a great need for comparative studies in which data are systematically compiled.

Laboratory populations

As a halfway house en route to applying analytic models to naturally occurring host-parasite associations, let us consider the artificial world of laboratory populations.

In the 1930s, Greenwood and his colleagues conducted a series of experiments on the way diseases can influence the dynamical behavior of populations of laboratory mice (*21*). Two infections were studied: a bacterial "mouse plague," *Pasteurella muris*, and a poxvirus, ectromelia. These experiments are remarkably detailed and well designed. Among other things, the cage space available to the mice was adjusted to keep the population density constant as absolute levels changed, thus avoiding complications arising from density dependences.

With one important exception, the mathematical model depicted schematically in Figure 1 may be used to analyze these host-parasite systems (*11*). The rates at which the numbers of susceptible, infected, and immune mice—$X(t)$, $Y(t)$, and $Z(t)$, respectively—change is described by a set of three differential equations, with the flows into and out of the three compartments being as indicated. The one important difference between Figure 1 and the actual experiments is that adult mice were introduced by the hand of the experimenter, at a constant rate of A adult mice per day, rather than by birth (as shown here). Susceptible mice are thus gained by "birth" or by recovered mice losing their immunity (at the per capita rate γ), and are lost by natural mortality (at the per capita rate b) or by acquiring infection. Both *P. muris* and ectromelia are transmitted directly, and we make the conventional epidemiological assumption that the net rate at which new infections appear is proportional to the number of encounters between susceptible and infected mice, βXY; the proportionality constant β represents the transmission rate. Thus infected mice appear at the net rate βXY and are lost by disease-induced mortality, by natural mortality, or by recovery into the immune class (at the per capita rates α, b, and v, respectively). The crucial difference between this system and conventional epidemiological ones is that the total host population, $N = X + Y + Z$, is not a predetermined constant but is itself a dynamic variable. In the absence of infection, A mice are added each day and bN are lost by natural deaths; the system thus settles to an equilibrium population, N^*, equal to A/b mice.

When N mice are in the cage, the intrinsic reproductive rate for the infection is

$$R_o = \beta N/(\alpha + b + v) \qquad (2)$$

This follows from the assumption that if one infected mouse were introduced into a population of N susceptibles, new infections would appear at the rate βN for the duration of the infection, which on average is $1/(\alpha + b + v)$. Equation 2 reduces to equation 1 if we define the threshold mouse population density as $(\alpha + b + v)/\beta$. From the earlier discussion, we see that *P. muris* or ectromelia infections can establish themselves among these mice provided the population exceeds the threshold density N_T. But the disease-free mouse population is $N^* = A/b$. Thus if the introduction rate A exceeds bN_T the infection can be established, and not otherwise.

Once the infection is established, the mathematical model predicts that the mouse population will settle to a new equilibrium value, below the disease-free level. This disease-regulated population density will increase linearly with increasing introduction rate, A.

In their experiments with *P. muris*, Greenwood and his co-workers introduced new mice at rates ranging from 0.33 to 6 mice per day. As can be seen in Figure 2, the ensuing equilibrium populations of mice indeed depended linearly on A, as suggested by the theory. In fitting the theoretical line to the observed data points, the transmission parameter β has been treated as an adjustable parameter. The critical introduction rate, bN_T, below which *P. muris* cannot be maintained appears to be 0.11 mice per day, corresponding roughly to an equilibrium population of 19 mice. Unfortunately, the experiments were never conducted at so low a rate, so this conclusion remains untested.

The researchers also investigated the dynamical behavior of the infected mouse populations, $N(t)$, as a function of time, t, for two particular introduction rates,

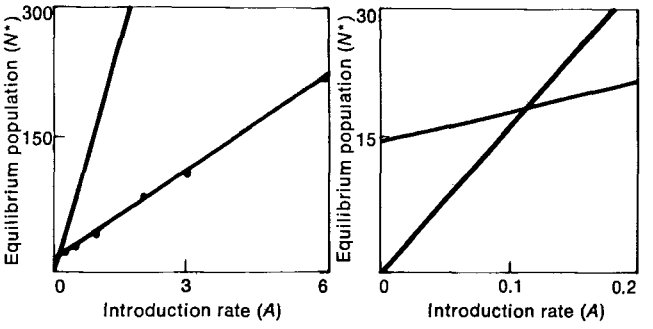


Figure 2. The equilibrium population of mice, N^*, is shown as a function of the introduction rate, A. The colored dots (*left*) represent the experimental results for populations infected with *P. muris*; the colored line indicates the relation given by a simple theoretical model, and the black line shows the relation in the absence of the infection. The intersection between the colored line and the black line – the disease-regulated and disease-free dependence of N^* on A, respectively – gives the critical rate of introduction, bN_T, below which *P. muris* cannot be maintained. An enlargement of the lower left-hand corner of the graph (*right*) suggests that the critical rate is 0.11 mice per day, corresponding roughly to an equilibrium population of 19 mice. (After ref. *11*.)

6 and 0.33 mice per day (Fig. 3). The theoretical curves here contain no adjustable parameters: the rates α, b, v, and γ can be estimated from independent studies of individual mice, while β (although it concatenates many biological and epidemiological factors in a way that defies direct estimation) is determined from Figure 2 as explained above. The agreement between the data and the theoretical curves, thus constructed, is encouraging.

The experiments with ectromelia were performed only for a single value of A, 3 mice per day. Consequently the analogue of Figure 3 now has one adjustable parameter (β). The fit between theory and data is again good. A comparison between the results for the bacterium *P. muris* and the virus ectromelia—which are biologically quite different organisms—is interesting, showing that the same basic mathematical model can apparently account for the essential dynamical features of both infections.

I have dwelt on this work for three reasons. First, it gives a hint of the kind of analysis that underlies the assertions in the next few sections. Second, it brings out some of the points about thresholds and regulation in an explicit fashion. Third, it shows that simple mathematical models can give a satisfactory account of observed facts, at least in the laboratory.

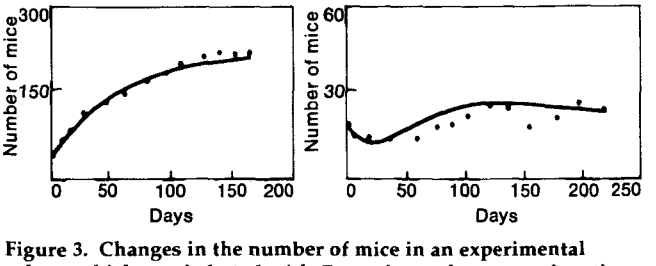


Figure 3. Changes in the number of mice in an experimental colony which was infected with *P. muris* are shown as a function of time for an introduction rate of 6.0 (*left*) and 0.33 (*right*) mice per day. The colored dots represent experimental observations, the colored lines the results of the simple theoretical model (in which all the parameters are estimated from other kinds of data). The agreement between theory and experiment suggests that the simple model does indeed capture the essentials of such a host-parasite association. (After ref. *11*.)

Natural populations

In the absence of infection, the host population depicted schematically in Figure 1 will grow exponentially at the per capita rate $r = a - b$, the difference between the per capita birth and death rates. Given this assumption of exponential growth, the host population will eventually exceed any threshold level for the establishment of a particular parasite. Under what circumstances may the additional mortality associated with the infection regulate the host population, holding it to some steady value? Under the simple circumstances represented in Figure 1 and assuming that the net transmission rate is βXY, the criterion for such regulation by a microparasite is (*11*)

$$\alpha > r[1 + v/(b + \gamma)] \qquad (3)$$

where α is the virulence, or disease-induced mortality rate, as defined above.

The assumptions on which equation 3 are based are excessively simple in many ways. Vertical transmission (whereby infection is transmitted from a parent to an unborn offspring, as happens in the case of many microparasites of insects) does not affect the criterion represented by equation 3, but does lower threshold population levels. Latent periods of significant length, during which infected individuals are not yet infectious, both raise thresholds and alter the criterion in a way that requires α to be larger. Microparasites that depress the reproductive capacity of infected hosts are effectively increasing α, and thus obviously find it relatively easier to satisfy the criterion for regulation. Dependence of the virulence on the nutritional state of the host, and a multitude of other possible density-dependent effects, make for further complications (*11*). The possibility that a macroparasite may regulate a host population can be similarly assessed, using a formula that is related to equation 3 (*14*).

Using equation 3 as a basic guide, we see that it will be easier for a host population to be regulated by a microparasite if the hosts have a relatively small r value, and if there is no acquired immunity (corresponding to $\gamma \to \infty$, whence the criterion for regulation is simply $\alpha > r$). This latter observation implies that, other things being equal, invertebrate populations may be regulated by parasites more commonly than vertebrates, which typically do possess acquired immunity against many infections. This marches with Holmes's empirically based suggestion that regulation may be more prevalent in invertebrate populations (*9*).

Among univoltine insects (where $\gamma \to \infty$ and r is not too large), there appear to be many instances of associations with viral, fungal, or microsporidian protozoan parasites which are candidates for regulating their host population (*22*). In particular, several baculovirus and microsporidian parasites found among univoltine forest insects are highly virulent and possess transmission stages during which the parasites live a relatively long time in the external environment, free of their hosts, thus helping the host-parasite association to persist. The outcome of such regulation of an insect population by a parasite population with long-lived transmission stages

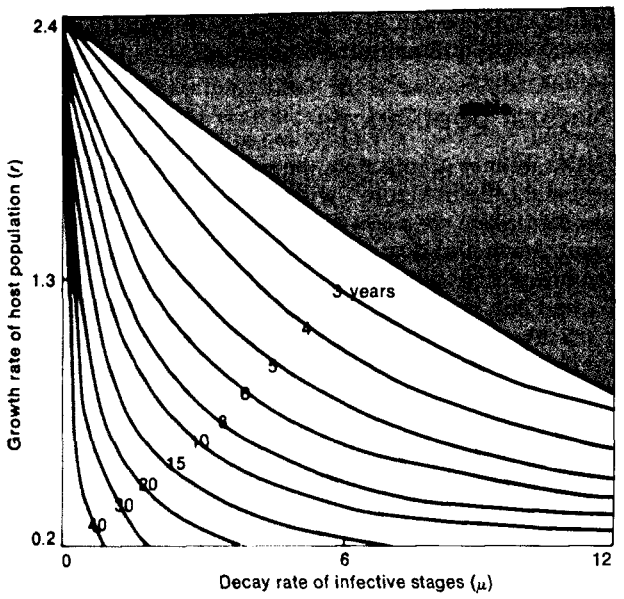


Figure 4. An association between a host population and a virulent parasite with free-living transmission stages can result either in a state of constant equilibrium or in stable cycles of varying length, depending on the intrinsic growth rate of the host (r) and the decay rate of the infective stages of the parasite (μ). In the upper right-hand corner of the figure, both r and μ are relatively high, leading to constant equilibrium values; at the lower left, r is relatively small and the transmission stages are long, resulting in cyclic periods ranging from a few years to a few decades, as indicated. (After ref. 22.)

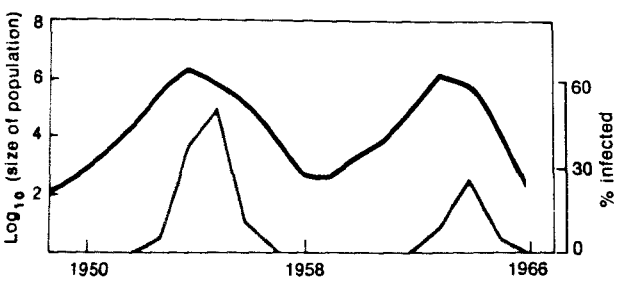
may be either a steady, constant value or a stable cycle in which the density of the host and the prevalence of disease rise and fall in a periodic fashion (22). Figure 4 illustrates how this range of outcomes depends on the intrinsic per capita growth rate, r, of the host insect population, and on the decay rate, μ, of the free-living infective stages of a parasite that is very virulent, so that $\alpha \gg r$.

Many univoltine forest insects have indeed been observed to exhibit such cyclic variations in abundance, with periods ranging from 5 to 12 years. In most cases, baculovirus or microsporidian pathogens have been found in these populations. But the possibility that the cycles are the result of host-parasite dynamics has only begun to be explored.

However, changes in the abundance of the larch budmoth, *Zeiraphera diniana*, in the Engadine Valley in Switzerland have been investigated in the light of the prevalence of infection with a granulosis virus in this population (23). As shown in Figure 5, all the main features of the data are in accord with the results of a theoretical model which is essentially that represented in Figure 1 (simplified by putting the recovery rate $v = 0$, and with the transmission process made complicated by accounting for the dynamics of the free-living infective stage of the parasite). Although this model explains both the 9- to 10-year period of the budmoth cycle and the pattern of prevalence of viral infection, it gives an amplitude of population oscillation that is an order of magnitude less than that observed. Other authors have explained the budmoth cycles as deriving from the interaction between this herbivore and the foliage it eats (24). I think the truth may lie in a combination of interactions, with the host-parasite dynamics setting the basic period and plant-herbivore effects enhancing the amplitude.

Such studies of the possible regulation of natural populations of invertebrates by viral, fungal, or protozoan parasites are of interest to those who seek a fundamental understanding of community dynamics. The studies may also eventually be useful in helping to specify the properties a pathogen should have, and in what quantities it should be distributed, to control an insect pest (22).

For an example involving vertebrate hosts, I turn to the current epidemic of rabies in Europe. This outbreak is thought to have originated in Poland in 1939, and is characterized by a high incidence in populations of red fox (*Vulpes vulpes*); of the roughly 17,000 cases of animal rabies reported in Europe in 1979, more than 70% were in this host species (25). Where rabies is now endemic in Europe, fox population densities appear to exhibit 3- to 5-year cycles around average levels that are significantly lower than the disease-free ones, which are set primarily by territoriality. An appropriately modified version of the host-parasite model described in Figure 1, allowing for a latent period in infected foxes and for density dependence in fox birth rates, indeed exhibits these dynamical features (26). Incorporating rate parameters estimated from field data on fox behavior and on the etiology of rabies in individual foxes, the model also helps explain the observed prevalence of infection in fox populations, and suggests a threshold density of around 1 fox per km^2 for maintenance of the infection (26). Such models may be applied to get a rough idea of



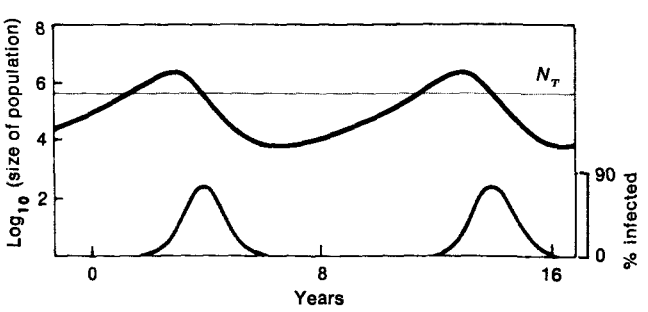


Figure 5. The observed patterns in the abundance of the larch budmoth, *Zeiraphera diniana* (*black line*), and in the prevalence of infection with a granulosis virus among this population (*colored line*), in the Engadine Valley in Switzerland from 1949 to 1966 are shown at the left. When the pertinent epidemiological and demographic parameters are used in a modified version of the model shown in Figure 1, the oscillations in the larch budmoth population in relation to the threshold level, N_T, and in the prevalence of infection are as indicated at the right. The theoretical model appears to give the correct period for the cyclic rise and fall of the budmoth population, although the actual oscillations have a larger amplitude than is predicted. (After ref. 22.)

the possibilities of controlling rabies by culling foxes or by vaccinating them with live baits.

General patterns

The preceding discussion has dealt largely with microparasitic infections, where it is usually possible to classify hosts simply as infected or uninfected. For macroparasitic infections, on the other hand, the damage inflicted on a given host individual usually depends strongly on the magnitude of the parasite burden.

Figure 6 illustrates the typical relation between the average number of macroparasites per host and the host population density, N, that emerges from mathematical models: below the threshold host density (N_T, corresponding to $R_o = 1$) the parasite cannot persist; as N increases above N_T, the average parasite burden at first increases markedly; and for very large N the average burden tends to saturate to a constant level as density-dependent effects exert their influences. If relatively high parasite burdens produce a sufficiently high degree of host mortality, then the relation shown in Figure 6 can lead to the parasites regulating their host population: at low host densities, there is little parasite-induced mortality, and the population grows; at high host densities, the average parasite burdens rise and cause many deaths, thus halting host population growth (*14*).

Laboratory and field studies have shown that the general theoretical relation depicted in Figure 6 is indeed found in real host-macroparasite systems. In the field—if the deep sea may be so called—Campbell and his colleagues (*27*) have demonstrated that the mean parasite loads in deep-living benthic fishes are directly related to the fish population densities. In addition, they found that more species of metazoan parasites occur when fish population densities are higher, which arguably is because such high host densities are above the threshold level for an increasing number of parasite species. Similar examples of an increase in the average number of parasites per host with increasing host density have been found in several ungulate species (*9*).

A related study, with broader implications, has been carried out by Freeland (*28*), who examined the protozoan parasites in the intestines of primates. Freeland's study embraced four primate species, and defies brief summary. One set of results showed that in social groups of mangabeys the number of protozoan species in a given individual increases systematically with the size of the group of which it is a member (Fig. 7). (This is not a sampling effect, because all individuals in a given social group exhibit identical protozoan faunas.) The explanation may be, in part, that suggested above for similar phenomena among fish. Freeland advances the idea that this increase in parasite infestation with increasing group size may influence the evolution of group size and of intragroup behavior. Thus parasites may affect not only the dynamics of their host population (the theme of my article), but also the behavioral ecology.

To summarize, the general relation shown in Figure 6 is found in real host-macroparasite associations. Such a relation, in conjunction with sufficiently high host mortality produced by high parasite burdens, can regulate the host population. There are, however, very few empirical studies of this question.

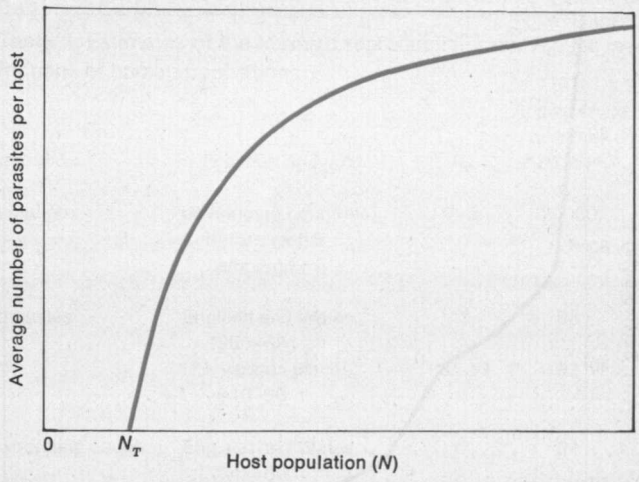


Figure 6. The theoretical relation between host population density and the number of macroparasites per host produces a characteristic curve which is supported by laboratory and field studies of real host-macroparasite systems. As the host density rises above the threshold level, N_T, the average parasite burden at first increases rapidly, but tends to rise fairly slowly or to settle to a steady value at very high values of N. At relatively high parasite burdens and correspondingly high levels of host mortality, this relation can lead to regulation of the host population by the parasite.

What fraction of all host deaths must be attributable to a particular microparasite or macroparasite, if the parasite is truly the regulator? A simple yet general answer can be given, provided only we assume that the per capita birth rate, a, and the per capita death rate from all other causes, b, are density-independent constants (which, of course, is not usually so):

$$\frac{\text{parasite-induced host deaths}}{\text{total host deaths}} = \frac{a-b}{a} \qquad (4)$$

The result holds for both microparasites and macroparasites, independent of the mode of transmission and of the nature of immune processes. If a and b are not too disparate, so that $(a-b)/a$ is small, the parasite can be responsible for regulating the host population, even though few deaths will be laid at its door. Conversely,

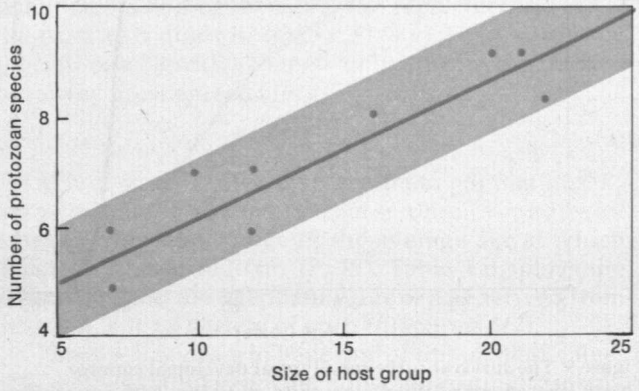


Figure 7. In a field study of mangabey social groups, the number of protozoan species exhibited by members of groups was found to rise systematically with increase in group size. Colored dots represent the observational data, and the colored line shows the best straight line that can be fit to the data; 95% of the results would be expected to fall within the shaded area if this linear fit is indeed significant. (After ref. *28*; © 1979 Ecol. Soc. of Am.)

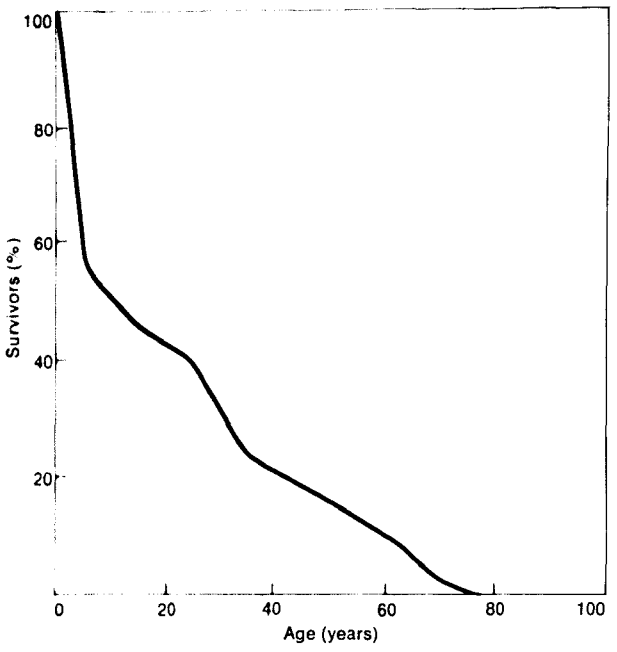


Figure 8. The survival curve for a group of hunter-gatherers who lived approximately 15,000 years ago on the Mediterranean coast shows high child mortality, with only about 50% of the population surviving past age 10. Although skeletal remains yield little definite evidence of parasitic infection, such a pattern suggests that this factor may have played a role. (After ref. *31*.)

if $a \gg b$ (as is the case for many invertebrates), the infection needs to be responsible for most of the observed mortality before it can be a candidate for consideration as the regulatory agent. My own equivocal view is that

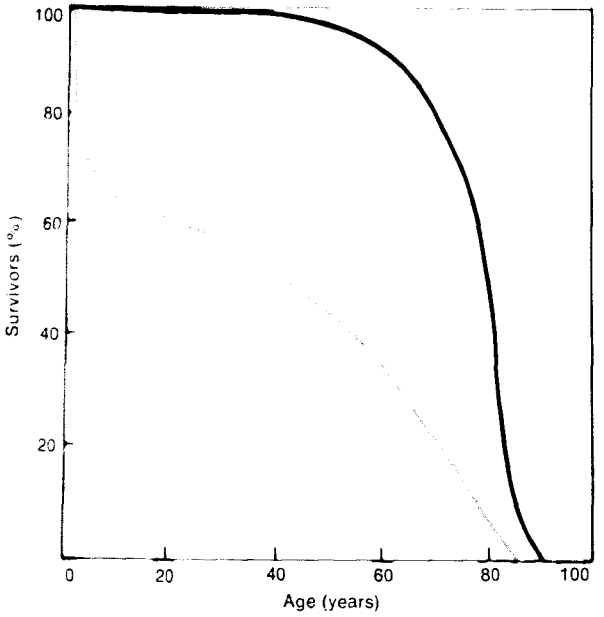


Figure 9. The survival curve for a typical developed country (*black line*) shows relatively low child mortality, with essentially all the population surviving to age 10, and more than 90% surviving past age 60. By contrast, the curve for a typical developing country (*gray line*) shows high child mortality, with only about 60% surviving past age 10, and less than 40% surviving past age 60; this higher mortality arises from a greater prevalence of parasitic infections combined, on average, with a lower nutritional state. (After ref. *38*.)

more often than not, no single factor can usefully be called *the* regulator.

Human populations

During most of the million or so years that humans have existed, their numbers have been low and relatively constant. The processes of fertility and mortality that kept this rough balance among hunter-gatherer populations are still far from understood (*29, 30*).

Figure 8 shows a survival curve, deduced from skeletal evidence (*31*), for a group of Mediterranean hunter-gatherers who lived about 15,000 years ago; this curve is probably fairly typical for such pre-agricultural groups (*29*). There is little doubt that diseases contributed to the mortality patterns exemplified by Figure 8, but precise knowledge of the extent of the contribution is impossible. Although some parasitic infections leave traces on early human skeletons—usually the only remains available for examination—most, particularly those caused by viruses and bacteria do not.

Certain conclusions may, however, be drawn from the discussion of threshold host densities given above. Bands of hunter-gatherers probably ranged in size from around 20 to at most 100 individuals (*29*), and these populations may have been sufficient to maintain many macroparasites as well as microparasites with long periods of infectiousness or (as is the case with hepatitis, herpes simplex, gonorrhea, and other infections) with asymptomatic carriers (*32, 33*). Pathogenic organisms whose normal habitat is a host other than man or that are able to multiply and survive successfully in soil and other inanimate environments (such as tetanus, gas gangrene, and other *Clostridiae*) could also play a role among these sparse early populations. But the directly transmitted microparasites responsible for much mortality in historical times—smallpox, measles, cholera, and the like—have very high host threshold densities, and could not have been present in the pre-agricultural era (*32, 33*).

Starting about 10,000 years ago in the Old World, nomadic cultivation began to give way to true agriculture, leading to denser and denser aggregations of people. Many macroparasites now undoubtedly began to attain infection levels that could produce morbidity and mortality (see Fig. 6). Zoonoses associated with domestic animals (such as tuberculosis) probably became significant. More important, population levels now became high enough for the virulent microparasitic infections to establish themselves. Many authors (*32–35*) have discussed the various consequences of these changing patterns in the relation between "plagues and peoples" (*36*).

One large pattern deserves more attention than it has received. According to Deevey's necessarily rough estimates (*37*), the first 5,000 years after the beginning of the Agricultural Revolution saw human numbers increase about twentyfold, from about 5 million to about 100 million. A second, roughly equal period, from about 5,000 years ago to 300–400 years ago, saw only about a fivefold increase, to approximately 500 million. A possible explanation is that human conglomerations gradually rose to levels capable of maintaining directly transmitted microparasitic diseases, whose effect was then to slow population growth.

A more familiar application of these ideas about threshold population sizes lies in the history of the Western European conquest of the New World and Oceania, which was accomplished largely with biological weapons: smallpox, tuberculosis, and measles. It seems likely the peoples of the New World and Oceania had no similarly virulent microparasites of their own with which to counter because they were, or until recently had been, at densities too low to maintain such infections. A notable exception that may have been exported to the Old World (although even this is debatable) is syphilis, which is well adapted to persist at low host densities.

Figure 9 contrasts modern survival curves for a developed country and a developing one (*38*). The comparatively high death rate in the Third World comes not primarily from exotic tropical diseases, but rather—especially in the first few years of life—from diarrhea, measles, and the like, combined with poor nutrition. The figure makes it clear, however, that infectious diseases continue to take a substantial toll in developing countries today. Moreover, both curves would tell a gloomier story if they were plotted for earlier times: the increases in life expectancy in the developed world over the past two centuries, and in the developing world since World War II, are due almost wholly to reduced mortality from infectious diseases (*39*).

Although this broad conclusion is plain, the details are difficult to elucidate. In Western Europe, mortality from microparasitic infections fell throughout the late eighteenth and the nineteenth centuries, long before the advent of modern drugs or vaccines (excepting that for smallpox). There is an unresolved argument about the relative contributions made by better nutrition, improved hygiene due to innovations ranging from more use of soap to better sanitation, and other factors (*40*, *41*). Similarly complex is the debate about the contribution made to overall population growth in European countries from about 1750 to 1850 by this decreased mortality, versus that made by increased fertility. Recent analyses suggest no single answer (*42*). In England, population grew mainly as a result of increased fertility, but with some help from declining mortality; in Sweden, population grew almost entirely as a result of decreased death rates, partly associated with smallpox vaccination; and in France, population remained roughly steady as mortality and fertility fell together.

In short, infectious diseases have been important sources of mortality throughout human history (*39*). In any epoch, however, their exact contributions to demographic trends are hard to pin down.

Control by vaccination

It is possible to be relatively precise about one technical aspect of the interplay between humans and directly transmitted microparasitic infections, namely the proportion of the host population that must be protected by an immunization program in order eventually to eradicate the infection.

We recall that a microparasite's intrinsic reproductive rate, R_0, is the number of secondary infections produced in a population where all are susceptible. Suppose now that a portion of the population, p, is protected by vaccination. The fraction remaining susceptible is at most $(1 - p)$, and, assuming that the host population mixes homogeneously, the reproductive rate of the parasite is diminished to $R_0(1 - p)$. For eradication, this rate must be driven below unity; that is, the fraction protected must exceed (*16*, *17*)

$$p > 1 - 1/R_0 \qquad (5)$$

For microparasitic infections in human populations, R_0 can be estimated accurately from serological studies, or roughly from knowledge of the average age at which infection is acquired (*16*, *17*, *43*). Table 1 displays the value of R_0, and the attendant value of p as derived from equation 5, for a variety of such infections (*43*).

Smallpox appears to have one of the smallest values of R_0 of these tabulated infections, suggesting that vaccination of around 70 to 80% of the population in the neighborhood of known cases may be sufficient for eventual eradication. This fact, in conjunction with the obviousness of the disease and the availability of an effective vaccine, may help explain the success of the global eradication campaign. Although the etiology of

Table 1. Estimates of the intrinsic reproductive rate, R_0, for infections of human populations

Infection	*Location and time*	R_0	*Approximate value of* p (%)[a]
smallpox	developing countries, before global campaign	3–5	70–80
measles	England and Wales, 1956–68	13	92
	US, various places, 1910–30	12–13	92
whooping cough	England and Wales, 1942–50	17	94
	Maryland, US, 1908–17	13	92
german measles	England and Wales, 1979	6	83
	West Germany, 1972	7	86
chicken pox	US, various places, 1913–21 and 1943	9–10	90
diphtheria	US, various places, 1910–47	4–6	~80
scarlet fever	US, various places, 1910–20	5–7	~80
mumps	US, various places, 1912–16 and 1943	4–7	~80
poliomyelitis	Holland, 1960; US, 1955	6	83
malaria (*P. falciparum*)	northern Nigeria, 1970s	~80	99
malaria (*P. malariae*)	northern Nigeria, 1970s	~16	94

SOURCES: See refs. *17* and *43*

[a] p = the proportion of the population that must be protected by immunization to achieve eradication

measles is similar to that of smallpox, with the infection always being apparent and running a relatively short course, the tentative estimate that R_0 is probably around 15 for measles in developing countries (corresponding to a p in excess of 93%) may make its global eradication much more difficult than was the case for smallpox.

The very high values of R_0 for malaria suggest that its eradication is likely to be very difficult, whatever the control method. In particular, a campaign against *P. falciparum* based wholly on the use of an effective vaccine would appear to require that 99% of the population be protected for eradication to be achieved.

Coevolution of host and parasite

The received wisdom, set forth in most medical texts and elsewhere, is that "successful" or "well-adapted" parasites are relatively harmless to their hosts. This idea is reasonable, at first sight: all else being equal, it is to the advantage of both host and parasite for the parasite to inflict little damage. Thus in regions of Africa where trypanosomiasis is endemic, indigenous ruminants suffer mild infections with insignificant morbidity, while domestic ruminants that have been bred for a long time in the region suffer more severely, and recently imported exotic ruminants suffer virulent infections which are usually fatal if untreated (*7*). The fact that parasitic infections appear to be more effective as regulatory agents among newly introduced species of plants and animals, or when the parasites are introduced into new regions, further supports this conventional view (*9*).

On theoretical grounds, it would indeed appear that parasites evolve to be avirulent, provided that transmissibility and duration of infectiousness are entirely independent of virulence. This assumption, however, is not generally valid; the damage inflicted on their hosts by viral, bacterial, protozoan, and helminth parasites is often directly associated with the mechanism by which the organism produces its transmission stages. Once these complications are introduced into the theoretical models, it appears that many coevolutionary paths are possible, depending on the details of the interplay between the virulence and the transmissibility of the parasite (*14, 22, 44–46*).

There are circumstances where the evolutionary pressures on the parasite may promote virulence. The various baculoviruses, which kill their insect hosts and effectively turn them into masses of viral transmission stages, are likely examples.

The introduction of the myxoma virus into wild populations of rabbits in Australia and England in the early 1950s provides an unusually well-documented and interesting case study (*47*). At first the disease was highly virulent, but throughout the subsequent decade successively less virulent strains of the virus began to appear. Since the mid-1960s, the virus appears to have come to an equilibrium with its rabbit host in both Australia and England, with the predominant strain of the virus being one of intermediate virulence. The data can be analyzed to get a rough estimate of the relationship between the virulence, α, and the transmission rate, $\beta(\alpha)$, and host recovery rate, $v(\alpha)$, of the various strains of the myxoma virus (*44*). Substituting these empirical relations for $\beta(\alpha)$ and $v(\alpha)$ in equation 2 for the intrinsic reproductive rate R_0 of myxoma virus, we obtain an estimate of the overall dependence of R_0 on α. In this particular instance, it turns out that strains with intermediate virulence, α, have the largest R_0, and may thus be expected to predominate (*44*).

In brief, although parasite "harmlessness" may characterize many old and established associations, neither a priori theoretical arguments nor empricial evidence point to this being a general rule.

The reader may conclude from this survey that empirical evidence about the extent to which natural populations of animals are regulated by parasitic infections is scattered and equivocal, and that theoretical models are largely still in a formative stage. I think this is an accurate impression. The general subject of the regulation of animal populations by parasites is, as yet, one in which there are more questions than answers.

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"We're insectivores. Spiders are arachnids. We don't eat them, and that's that."