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HOST POPULATION STRUCTURE AND THE EVOLUTION OF VIRULENCE: A "LAW OF DIMINISHING RETURNS"

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Abstract.—Structure in a population of host individuals, whether spatial or temporal, can have important effects on the transmission and evolutionary dynamics of its pathogens. One of these is to limit dispersal of pathogens and thus increase the amount of contact between a given pair or within a small group of host individuals. We introduce a "law of diminishing returns" that predicts an evolutionary decline of pathogen virulence whenever there are on average more possibilities of pathogen transmission between the same pair of hosts. Thus, the effect of repeated contact between hosts will be to shift the balance of any trade-off between virulence and transmissibility toward lower virulence.

Key words.—evolution, virulence, parasites, pathogens, population structure, pathogenicity, transmission.

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There is a growing literature on the relation between the transmission of pathogens and the evolution of their virulence (Anderson and May 1979, 1981, 1982, 1991; May and Anderson 1983; Levin and Pimentel 1981; Bremermann and Pickering 1983; Ewald 1983, 1991, 1993; Fenner 1983; Stewart and Levin 1984; Bremermann and Thieme 1989; Knolle 1989; Levin and Svanborg Eden 1990; Nowak 1991; Bull et al. 1991; Frank 1992; Herre 1993; Antia et al. 1994; Lenski and May 1994; Nowak and May 1994).

The longstanding evolutionary "conventional wisdom" has been that parasites should evolve to be relatively benign to their hosts (Burnet and White 1972; Allison 1982; McKeown 1988); in contrast, the aim of the recent works cited above has been to define the conditions under which natural selection might favor increased levels of parasite virulence. When all other things are equal, parasites lose opportunities for continued reproduction and transmission when they kill their host; thus, these studies have looked for some compensatory benefit of higher virulence that would allow highly virulent strains to persist in the population. Several possible advantages of virulence have been proposed as candidates to offset the disadvantage of increased host mortality. These include: resistance to immune clearance (Fenner and Ratcliffe 1965; Anderson and May 1982); within-host competitive advantage (Levin and Pimentel 1981; Herre 1993; Nowak and May 1994); and increased transmissibility.

Virulence has a number of different and sometimes contrasting meanings (Garnick 1992); specialized meanings are particularly frequent in the plant and medical literatures. Since host killing presents the most obvious evolutionary problem, the disease-induced death rate has been the most common meaning of virulence in evolutionary studies. The present paper is concerned with the evolution of the disease-induced death rate, as well. Where other forms of virulence are discussed below, they are clearly distinguished.

Increased transmissibility is probably the best-documented correlate of increased virulence that can help to explain the maintenance of highly virulent strains. Studies have revealed that highly virulent strains are also more transmissible for such diverse pathogens as myxoma virus (Andrewes 1960; Mead-Briggs and Vaughan 1975); *Pasteurella muris* bacteria (Greenwood et al. 1936); *Plasmodium falciparum,* one of the parasites that cause malaria (Day et al. 1993); barley yellow dwarf virus (reviewed in Power 1992); and possibly the human immunodeficiency viruses (DeCock et al. 1993). This is not surprising, since for many pathogens, both the severity of disease and the likelihood of transmission per unit time depend on the level and rate of replication of the pathogen within the individual host.

For reasons of tractability and conceptual clarity, most studies of the evolution of virulence have assumed that transmission is both random and well-mixed (Ewald 1991 and Herre 1993 are exceptions); no spatial or temporal structure in the host population is assumed.

Yet there is good reason to believe that structure is ubiquitous in natural populations. The dispersal of plant pathogens, for example, is spatially limited by the range of the dispersing agent (wind, animal vector, etc.). Human and animal populations, too, disperse their pathogens over a more or less limited area, depending on their mobility and on the interaction between the hosts' behavior and the means by which the pathogens travel from one host to another. In sexually transmitted diseases, the degree of partner fidelity in the host population imposes a kind of structure on the population; in repeated sexual contacts, additional propagules of a pathogen will be transmitted to hosts who may already have received some of that pathogen's propagules.

A population of monogamous couples with long periods of partner fidelity, then, is a highly structured population from the perspective of a sexually transmitted pathogen. A waterborne pathogen that disperses over long distances, on average, between one individual and the next, would be spreading in a relatively unstructured population. As these examples show, structure is in the eye of the infector: the effective degree of structure in the host population depends not only on the hosts' behavior, but also on the dispersal mechanism of the pathogen.

This paper assesses the effect of one aspect of host population structure—the repeated transmission of propagules of

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the same pathogen from one infected individual to the same susceptible individual—on the evolution of virulence. We assume that the evolution of virulence is directed by a trade-off between infectiousness and virulence: that is, strains that produce extra propagules and are therefore more transmissible do so at the expense of killing their hosts more quickly. We further assume no vertical transmission and no superinfection; for the effects of these complexities on the evolution of virulence, see Nowak (1991), Yamamura (1993), Nowak and May (1994) and Lipsitch et al. (1995).

Under these assumptions, we propose a "law of diminishing returns," which predicts that increased transmission opportunities between the same pair of hosts will lower optimal parasite virulence. Thus, if all else is equal, populations in which the same hosts have repeated or long-term contact should favor parasite strains with a lesser degree of virulence than less structured ones.

Model

Consider a population of hosts in which uninfected individuals have a natural death rate μ, whereas infected individuals die at the increased rate $\mu + v$. The parameter v gives the disease-induced death rate, which we call the virulence of the parasite. Additionally, infected individuals may recover at the per capita rate γ to become immune. We allow for the possibility that $\gamma = \gamma(v)$—there may be a relationship between the mortality rate and the recovery rate, and we put no constraints on this relationship. Let $r(v)$ denote the probability that an uninfected individual will become infected by a single contact with an infected individual. We assume that r increases with v, that is, more-virulent strains are more transmissible. Let n be the average number of contacts (or the average duration of a partnership) between members of a host pair. As long as the average duration of a partnership is much less than the duration of the infection, we can assume that n is independent of v. Then the probability of infection per partnership is $\beta(v) = 1 - a^n(v)$, where $a(v) = 1 - r(v)$.

The basic reproductive number of a parasite (Anderson and May 1982) can be defined as $R_0 = N_0 c\beta(v)/[\mu + v + \gamma(v)]$. R_0 simply denotes the average number of secondary infections caused by a single infected individual if introduced into an uninfected population. Here N_0 is the density of susceptible individuals in an equilibrium population in the absence of infection, c is the rate of acquiring new partners or making new contacts, and $[\mu + v + \gamma(v)]^{-1}$ is the average lifetime of an infected individual. Under a variety of conditions (but excluding superinfection and vertical transmission; Nowak 1991; Nowak and May 1994), competition among strains of parasites favors the strain with the highest R_0 (Anderson and May 1981, 1991; Bremermann and Thieme 1989).

We are interested in the effect of n on the optimal level of virulence, v^*, which maximizes R_0. As n increases, the probability $\beta(v)$ converges faster to 1, as shown in figure 1A. Because of these diminishing returns at high values of n, further increases in virulence produce only very small increments in the probability of transmission to the partner. The increase in transmission is too small to offset the effects of faster host mortality. Thus, $R_0(v) \propto \dfrac{c\beta(v)}{\mu + v + \gamma(v)}$ reaches its maximum for lower values of v. Increased transmission opportunities between the same host pair reduce the optimal level of virulence. Figure 1B shows the relation between v and R_0 for different values of n, and a formal proof of this argument is given in the appendix.

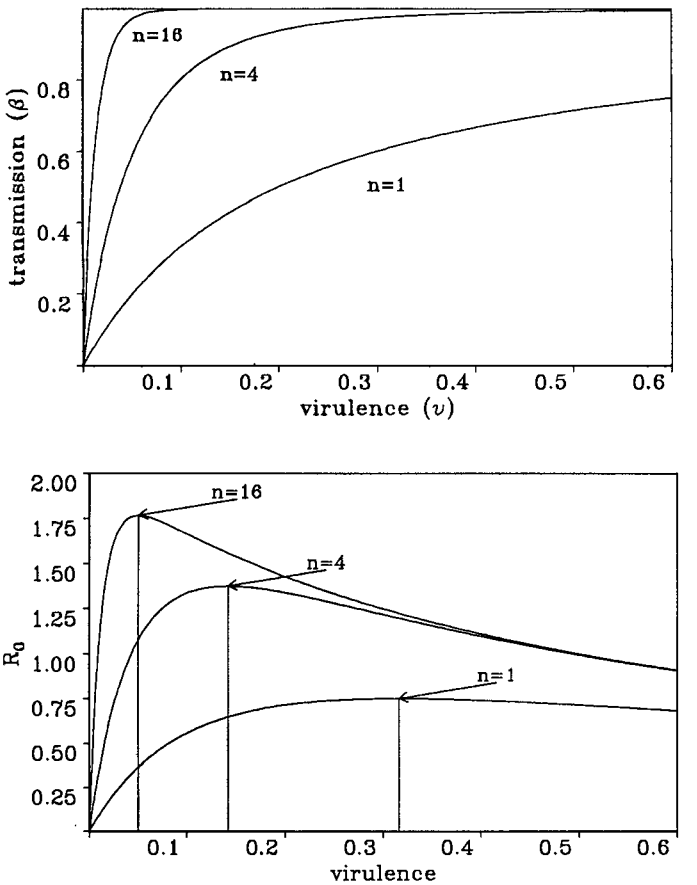

FIG. 1. A "law of diminishing returns" for pathogen virulence: as the number of contacts between a pair of hosts increases—which is most likely in highly structured populations—pathogens should evolve to be less virulent. Top. For higher numbers of contacts per pair of hosts, the transmission rate saturates more rapidly. Here transmission rate (β) is plotted against virulence (v) for three values of n (number of contacts per host pair). Bottom. As number of contacts per host pair (n) increases, basic reproductive rate (R_0) reaches its optimum for lower values of virulence (v). Vertical lines are drawn at values of v that maximize R_0 Shown are curves for n = 1, 4, and 16. Parameters: $r(v) = 5v/(1 + 5v)$; $R_0 = (1 - [1 - r(v)]n)/(.5 + v)$.

Discussion

This model is formulated in terms of the balance between the loss of transmission opportunities caused by shortened host life span and the increase in transmissibility presumably caused by higher levels of the parasite within the host. Thus, it is most directly applicable to parasites whose principal form of virulence is killing the host. However, virulence can take other forms as well, the most serious of which, from the host's point of view, is loss of fecundity. In general, this form of virulence, although disastrous for the host, is not surprising from the point of view of the parasite; it may, in fact, be a

survival strategy (Badouin 1975; Obreski 1975). It is for this reason that most models of the evolution of virulence have focused on explaining why parasites kill their hosts, which poses an obvious evolutionary dilemma.

However, in certain cases, this model is applicable to reduced host fecundity as well. When parasites are commonly transmitted from parent to offspring (vertical transmission), reductions in host fecundity also reduce the number of new infected hosts for the parasite. More generally, whenever virulence results in a loss in transmission opportunities for the parasite, there is an evolutionary question of why virulence is maintained. If the compensating benefit is an increase in the probability of transmission for any given contact, diminishing returns may be important.

One possible example of the operation of diminishing returns when virulence takes the form of reduced fecundity is the interaction of fig wasps and their nematode parasites studied by Herre (1993). This study examined 11 species of wasps, each of which lays its eggs in, and simultaneously pollinates, an associated species of fig. Each species of wasp is also parasitized by an associated species of nematode, which hatch from the foundress wasp inside the fig and infect the next generation of wasps. It was shown that the parasites of wasps that colonize figs that routinely contain many wasp foundresses are more virulent than the parasites of wasps that colonize figs containing only one foundress. In these associations, virulence takes the form of reduced fecundity of infected wasps relative to uninfected wasps.

Herre (1993) offered two explanations for this observation. First, figs with few wasp foundresses ensure a high degree of vertical transmission of parasites, closely tying the fitness of the nematodes to that of their hosts, and thus raising the cost of virulence for the parasite. Second, in the broods of wasp species that routinely hatch in low-foundress-number figs, competition to infect wasps of the next generation is more likely to be between related nematodes, and this creates a situation in which there is less selective advantage for nematodes to produce many infectious offspring.

Diminishing returns offers a third explanation of these observations, one that is compatible with the two previously proposed. Figs with fewer foundresses, in general, produce fewer wasp offspring (Herre 1989). If more virulent nematodes produce relatively more offspring nematodes (which then infect the new generation of wasps), then there is an increasing relationship between virulence and transmissibility. But in figs containing few wasps, a nematode producing additional offspring is more likely to waste them on young wasps that it has already infected, than in figs that have many foundresses and thus more young wasps. Thus, in fig species that typically have few foundresses, the advantage of greater virulence diminishes more rapidly, and the optimal level of virulence is lower.

We have emphasized that repeated contacts between the same hosts over time should lower optimal virulence. Further, we believe that aggregation in space is likely to have similar effects. For example, if the parasites inside an infected host produce a fixed number of propagules, and if these propagules compete strongly with one another to infect a few uninfected individuals, then the optimal virulence should be lower than that for well-dispersed propagules.

Sophisticated epidemiological models generally include various effects of host population structure in their analysis of the spread of parasites and pathogens, and there is a large literature describing how departures from "well-stirred" transmission dynamics affect the spread of disease. For example, May and Anderson (1987) showed that heterogeneities in rates of sexual partner change increase the "effective" rate of sexual transmission of a pathogen over the simple average rate because individuals who change partners rapidly contribute a disproportionate share to total transmission. As a result, the rate of new infections in the population is proportional to the sum of the mean and the ratio of the variance to the mean. Recent simulations (Hassell et al. 1991) have considered the effects of spatially structured host populations and spatially limited parasitoid dispersal on the dynamics of host-parasitoid populations. The principle of diminishing returns extends this work by considering the effects of population structure in an evolutionary context.

Population structure is also known to change the direction of selection between mutualism and parasitism in other areas. Diminishing returns should be distinguished from other effects of population structure that also affect the evolution of virulence. Axelrod and Hamilton (1981) noted that long-term associations between two individuals tend to promote mutualistic interactions; this was the basis for the emergence of cooperation in their experiments with the repeated prisoner's dilemma. This effect, however, concerns the association between host and symbiont, not the association between two hosts during which they transmit symbionts. More recently, Nowak and May (1992, 1993) showed that spatial structure in populations can evoke the evolution of cooperation because individuals tend to interact with their neighbors, which are likely to resemble them. In a similar vein, Chao and Levin (1981) found that the emergence of anticompetitor cooperation in the form of bacteriocin production is enhanced by spatial structuring of the bacterial population (however, we use the term cooperation guardedly, since bacteriocin production is cooperative only from the perspective of other bacteriocin carriers). The latter studies differ from diminishing returns because, at least from one perspective, they concern only hosts, and no symbionts (again, this description might be controversial in the case of bacteriocins, but nonetheless points to a real distinction between the two effects). All of these studies point to the same conclusion: population structure can change the outcome of evolution; in these cases, at least, spatial structuring seems to promote cooperative behavior.

Ewald (1991) has hypothesized that increased "sexual contact diversity" in the host population should promote the evolution of more virulent sexually transmitted parasites. His measure of diversity is not specified, although it includes both the number of partners and the number of contacts with each partner. This paper suggests, on the contrary, that in the long run, repeated contact with the same partner selects for *less* virulent strains. It is important to distinguish this effect from the effect of faster acquisition of new partners, which in the notation above would be an increase in c. Two of us (Lipsitch and Nowak 1995) have shown that increases in c may increase, decrease or leave unaffected the optimal vir-

ulence of a parasite, depending on the precise epidemiological and demographic circumstances.

The effects discussed here are an example of the nonlinear effects of changes in the degree of population structure on the relationship between transmission rate and virulence. Changes in a host population—such as increased mobility—or changes in a parasite—such as improved dispersal or vector transmission—may spread the propagules of a parasite more evenly, lowering the effective degree of population structure experienced by the parasite. This in turn should relax the selection against more virulent strains and may cause an increase in the virulence of the parasite. Likewise, a sexually transmitted disease endemic in a population with long partnerships between individuals should, if all else is equal, be less virulent than one spreading in a population characterized by casual encounters, even if the rate of acquiring new partners is the same.

This paper makes several simplifying assumptions. The most important of these is that there is an increasing relationship between virulence and transmissibility. This assumption is accurate for a wide range of parasites, as described above. However, the relationship is probably never perfectly increasing; there will likely be strains of many parasites that are both less transmissible and more virulent than competing strains. Such strains are likely to be of little evolutionary interest, however, as they will be inferior competitors regardless of host contact patterns and population structure (unless they have some other, compensating advantage). The effect of diminishing returns is to reduce the importance of differences in transmissibility between strains; in the general case in which strains differ in many characteristics, this effect will still hold. For example, the conclusions of our model are unaffected by the presence or absence of a functional relationship between virulence (ν) and recovery rate (γ). Moreover, our results agree with those of Sasaki and Iwasa (1991), who have shown using an optimal control model that when the viral load-transmission function is saturating (less than linear increase in β with respect to viral load), persistent strains gain a selective advantage at the epidemiological level compared to highly virulent, fast-replicating strains. If virulence and viral loads are closely related, as seems likely, then repeated contacts create just such a rapidly-saturating function (see fig. 1A).

We have also assumed that virulence is a characteristic of the parasite; in nature, genetic variation in hosts and environmental differences will produce a range of virulence for any given parasite strain. Since parasites generally have faster generation times and higher mutation rates than their hosts, it is likely that much of parasite evolution can be approximated by assuming a constant environment, where the environment includes the genetic makeup of the host population. Thus the virulence referred to here should be thought of as an average value for the strain of parasite in a given environment. However, it is in principle quite possible to incorporate the idea of diminishing returns, in its present mathematical form, into more complex, host-parasite coevolution models.

A final assumption that should be emphasized is that infection by one strain of the parasite precludes further coinfection or superinfection by another strain. Empirical observations (Herre 1993) and theoretical treatments (Levin and Pimentel 1981; Bremmermann and Pickering 1983; Nowak and May 1994; van Baalen and Sabelis 1995) strongly suggest that either coinfection or superinfection of individual hosts should result in a higher level of virulence.

We have modeled the effect of repeated contact between pairs of hosts as the simplest and smallest-scale form of population structure. However, any population that is subdivided so that individuals have many potential transmission events with some fraction of the population—other members of a family, a band of hunter-gatherers, or a class of schoolchildren, in the case of human pathogens—should produce a situation of diminishing returns for the pathogen. It has been suggested that highly virulent pathogens can spread only in large populations; the phenomenon of diminishing returns suggests an additional reason why disrupting population structure and increasing the degree of mixing among subpopulations is likely to favor more virulent pathogens. However, further work remains to be done to treat this more general situation formally, and to include the effect of diminishing returns in spatially structured epidemiological and evolutionary models.

More general studies of evolutionary epidemiology in structured populations may demonstrate new phenomena that do not arise in the limited case considered here. We have shown that one effect of population structure—repeated contact between the same hosts—should, all other things being equal, decrease the expected virulence of parasites. Other effects might either increase or decrease parasite virulence. For example, spatial structure disrupts random mixing by limiting transmission to other hosts "near" a particular host. Spatially limited dispersal should create local host shortages in areas of high infection, thereby favoring less virulent strains that can maintain their infections for a long time. On the other hand, the same local limitation of hosts should select for strains that will quickly infect whatever uninfected hosts become available; this should favor more virulent strains. Analyzing the net effects of these opposing pressures is an important direction for future research.

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Appendix

The proof is in two parts. First, we show that as n increases, each local maximum of R_0 moves to the left. Next we prove that as n increases, no new global maximum arises to the right of the old global maximum. Thus, for increasing n, the global maximum moves to the left.

The basic reproductive rate can be written as a function of virulence, v, and number of contacts per partnership, n, as follows:

$$R_0(n, v) = \frac{c(1 - a^n)N_0}{\mu + v + \gamma}, \tag{1}$$

where $a = 1 - r(v)$, as above. To obtain the virulence, v_m, that maximizes R_0 for a given value of n, we set $dR_0/dv = 0$ and obtain

$$a_m^{n-1}(b_m n + a_m f_m) = f_m, \tag{2}$$

where $R_0(n, v)$ has a local maximum at v_m, $a_m = 1 - r(v_m)$, $b_m = (\mu + \gamma_m + v_m)r'(v_m)$, and $f_m = 1 + \gamma_m'$; primes (′) indicate the derivative with respect to v. We want to show: as n increases, the local maximum of R_0 occurs for lower values of v. For this it is sufficient to show that $(dR_0(n + 1, v)/dv > 0$, which is equivalent to

$$a_m^n[b_m(n + 1) + a_m f_m] < f_m.$$

Using equation 2, this can be rewritten

$$f_m + \frac{f_m(1 - a_m^n)}{n} < \frac{f_m}{a_m}.$$

Note that f_m is the derivative of the denominator of R_0 with respect to v. If f_m were negative, then R_0 could not reach a maximum at v_m, since its numerator would be increasing and its denominator decreasing. Thus, f_m must be positive, and we can divide the inequality by f_m, substitute for a_m, and obtain

$$1 - (n + 1)r < (1 - r)^{n+1}.$$

This is the Bernoulli inequality, so the proof is complete. By induction, the local optimum moves to the left for every $n_1 > n$.

We have shown that each local maximum $R_0(v_m)$ is replaced by a maximum at a smaller value of v as n increases. Next, we show that if $R_0(n,v_g)$ is the global maximum for a given n, then no new optimum appears to the right of v_g for $n_1 > n$.

Since v_g maximizes R_0,

$$R_0(n_0, v_g) = c\frac{1 - a_g^n}{\mu + v_g + \gamma_g}N_0 > c\frac{1 - a^n}{\mu + v + \gamma}N_0 = R_0(n, v),$$

for all $v > v_g$, where v_g maximizes R_0 for a given n. Here $a_g = 1 - r(v_g)$. This is equivalent to

$$\frac{1 - a_g^n}{1 - a^n} > \frac{\mu + v_g + \gamma_g}{\mu + v + \gamma}. \tag{3}$$

It can be shown by induction (for integer n) that if $v > v^*$, then

$$\frac{1 - a_g^{n+1}}{1 - a^{n+1}} > \frac{1 - a_g^n}{1 - a^n}. \tag{4}$$

This can be rewritten

$$\frac{1 - a_g^{n+1}}{1 - a_g^n} > \frac{1 - a^{n+1}}{1 - a^n}. \tag{5}$$

The inductive proof is as follows. Since $v > v_g$, we know that $a < a_g$. From this it follows that

$$\frac{1 - a^2}{1 - a} < \frac{1 - a_g^2}{1 - a_g}.$$

Thus, inequality 4 is true for $n = 1$.

For the induction, we assume that

$$\frac{1 - a_g^n}{1 - a_g^{n-1}} > \frac{1 - a^n}{1 - a^{n-1}} \tag{6}$$

and show that inequality 4 is true in general.

Taking the negative reciprocal of both sides of inequality 6 (which leaves the inequality sign the same), and adding 1 to each side, we have

$$\frac{a_g^{n-1} - a_g^n}{1 - a_g^n} > \frac{a^{n-1} - a^n}{1 - a^n}.$$

Both sides of this inequality are positive, and $a_g > a > 0$. Thus we can multiply the left by a_g and the right by a, to obtain:

$$\frac{a_g^n - a_g^{n+1}}{1 - a_g^n} > \frac{a^n - a^{n+1}}{1 - a^n}.$$

Adding 1 to both sides gives inequality 4, completing the inductive proof.

Combining inequalities 3 and 4 and rearranging,

$$R_0(n + 1, v_g) = c\frac{1 - a_g^{n+1}}{\mu + v_g + \gamma_g}N_0 > c\frac{1 - a^{n+1}}{\mu + v + \gamma}N_0 = R_0(n + 1, v),$$

for all $v > v_g$. By induction, this is true for any $n_1 > n$.

We have shown that $R_0(n_1,v) < R_0(n_1,v_g)$ for all $v > v_g$, so as n increases, R_0 can have no global maximum to the right of the old global maximum v_g. Combined with the first half of the proof, which showed that each local optimum moves to the left as n increases, we have shown that the global optimum moves to the left as n increases.