MODELS OF PARASITE VIRULENCE

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ABSTRACT

Several evolutionary processes influence virulence, the amount of damage a parasite causes to its host. For example, parasites are favored to exploit their hosts prudently to prolong infection and avoid killing the host. Parasites also need to use some host resources to reproduce and transmit infections to new hosts. Thus parasites face a tradeoff between prudent exploitation and rapid reproduction—a life history tradeoff between longevity and fecundity. Other tradeoffs among components of parasite fitness also influence virulence. For example, competition among parasite genotypes favors rapid growth to achieve greater relative success within the host. Rapid growth may, however, lower the total productivity of the local group by overexploiting the host, which is a potentially renewable food supply. This is a problem of kin selection and group selection.

I summarize models of parasite virulence with the theoretical tools of life history analysis, kin selection, and epidemiology. I then apply the theory to recent empirical studies and models of virulence. These applications, to nematodes, to the extreme virulence of hospital epidemics, and to bacterial meningitis, show the power of simple life history theory to highlight interesting questions and to provide a rich array of hypotheses. These examples also show the kinds of conceptual mistakes that commonly arise when only a few components of parasite fitness are analysed in isolation. The last part of the article connects standard models of parasite virulence to diverse topics, such as the virulence of bacterial plasmids, the evolution of genomes, and the processes that influenced conflict and cooperation among the earliest replicators near the origin of life.

INTRODUCTION

SOME PARASITES exploit their hosts in a prudent way, taking the resources that they need without causing noticeable damage. Prudent exploitation yields sustainable benefits to the parasite as long as the host remains healthy. Other parasites attack their host more quickly and vigorously. Rapid exploitation may allow the parasites to achieve higher reproductive rates, but damage to the host reduces the parasites' opportunity for sustainable yield.

Following this economic line of thought, each parasite faces a tradeoff when increasing the rate at which host resources are used. Greater exploitation has the benefit of more rapid reproduction and transmission to new hosts, but carries the cost of reducing the host's ability to procure more resources in the future. For each host-parasite interaction, there may be a particular optimum schedule of host utilization that maximizes the parasites' balance between rapid transmission and the time before the host dies (Fenner et al. 1956; Levin and Pimental 1981; Anderson and May 1982; Levin 1983; Ewald 1983).

Simple economic considerations will certainly not explain all aspects of parasitism and the severity of disease (virulence). Nonetheless, a great deal can be learned by analysing how parasite fitness is influenced by the costs

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and benefits of host exploitation. The tradeoff between transmission and virulence is one example. I will briefly mention a second example and then outline the specific goals for this article.

One process missing from the tradeoff between transmission and virulence concerns the "social" aspect of parasite interactions. Suppose that prudent exploitation of a host maximizes a parasite's fitness. Selection then favors each parasite genotype, when alone in a host, to follow the prudent strategy. There is, however, a problem when two or more genotypes occupy the same host. If one genotype extracts host resources rapidly and reproduces quickly, then the host may die in a short time. A prudent genotype would have relatively low fitness when paired in a host with a rapacious genotype because, for both genotypes, the host is short-lived, and the rapacious genotype reproduces more rapidly than the prudent one.

The problem of competing for a shared, limited resource is, colloquially, the "tragedy of the commons" (Hardin 1968, 1993). The shared resource may be used most efficiently by slow, prudent exploitation, but rapacious individuals can gain a disproportionate share of the total by rapid exploitation. Each parasite gains most by balancing the benefit from rapid exploitation and the cost of reducing the total resource (Lewontin 1970; Levin and Pimental 1981).

I will analyse the problem of relative gains within the group versus total productivity of the group by using the well known theories of kin selection and group selection (Hamilton 1964a,b, 1975). Closely related parasites are favored to cooperate and exploit their host prudently, whereas distantly related parasites are favored to compete intensely. Thus multiple infection, with many competing genotypes and low relatedness, favors rapid exploitation and high virulence (Hamilton 1972; Bremermann and Pickering 1983).

This kin selection theory for exploitation of hosts extends the economic framework of tradeoffs to cover the "social" component of cooperation and competition among parasites. From this point of view, models of virulence fit easily into the standard theories of social evolution and life history evolution that have been developed extensively in the past few decades (Andersson 1984; Stearns 1992). More importantly, this broad view of virulence allows a number of unsolved problems in the origin and evolution of genetic systems (Szathmáry 1989a) to move into the framework of life history and social evolution (Frank 1994a). For example, the first protocells in early evolution probably contained several copies of replicator molecules. Each trait of those replicators is selected according to the balance between individual benefit from rapid exploitation and group benefit from prudent exploitation. In other words, the problem of cooperation versus conflict in early evolution is the problem of the evolution of virulence.

Models of virulence apply whenever individuals share a limited resource that can be exploited prudently or used up quickly for rapid, short-term benefits. My favorite slogan along these lines is "selfish DNA with self-restraint." This is the title of a news article about transposons published in the journal *Nature* (Doolittle et al. 1984). Transposons, which are related to viruses, form a special class of DNA sequences that have been inserted into the host's genome. They replicate within the host by copying themselves and inserting the copy in a different place. Too many copies of the transposon can damage the host. Some transposons appear to regulate their copy number by a biochemical feedback process (Kleckner 1990). Thus they are "selfish" because they spread as parasites within the host, and they have "self-restraint" because they exploit the host prudently. The models for virulence that I develop here provide the necessary background for studying transposons, protocells, and other problems of genome evolution.

The evolution of virulence is a rapidly growing field of research. Several reviews have appeared recently. In particular, Ewald (1994), Garnett and Antia (1994), and Bull (1994) have provided overviews of the field, including history, current theory and recent applications. I recommend these papers, particularly for the history and for examples from different parasites.

I focus here on developing a formal structure for adaptive tradeoff theories. These tradeoffs include transmission versus viru-

lence, competition within and among hosts (kin selection), and other tradeoffs that arise naturally in the study of parasite life history. I also consider when the dynamics of epidemics favor increased or decreased virulence. In the second part of this article, I analyse recent theories and applications in light of the formal conceptual structure. My analysis shows that, even with simple tradeoff theories, considerable understanding and care are needed to develop predictions for specific systems. Finally, I connect standard models of parasite virulence to diverse topics, such as the virulence of bacterial plasmids, the evolution of genomes, and the processes that influenced conflict and cooperation among the earliest replicators near the origin of life.

THE VALUE OF SIMPLE TRADEOFF THEORIES

Tradeoff theories suggest that the main features of life history evolution can be understood by simple economic arguments. But two problems arise when applying these simple theories. First, real parasites often appear to perform poorly on an economic scale. Second, the theory itself is deceptive—the assumptions are very simple but the consequences are often surprising. I discuss these two problems briefly before turning to the theory in the next section.

The first problem is illustrated by Levin and Bull's (1994) criticisms of tradeoff theories. They suggest that many infectious parasites cannot be understood through economic analysis. I briefly outline their arguments concerning bacterial meningitis (more details are given below) to show the difficulties that can occur when applying the theory to real cases.

The species that cause meningitis are typically harmless. They colonize the nasopharyngeal passage and are transmitted by droplet infection. Rarely, a few bacteria circulating in the blood manage to cross into the cerebrospinal fluid and expand into a severe and often fatal infection. The bacteria are unlikely to be transmitted to another host from the cerebrospinal fluid. Meningitis appears to contradict the tradeoff theory; high virulence is correlated with poor transmission.

There are two interpretations for this contradiction. First, high virulence occurs because of mutation and selection of bacterial populations within hosts (Levin and Bull 1994). Any bacterial mutant that increases its reproductive rate will spread within hosts regardless of the long-term consequences for bacterial fitness. Thus high virulence occurs because of within-host evolution and has nothing to do with tradeoffs between virulence and transmission. However, it is important to keep in mind that natural selection influences the statistical distribution of traits in a population. The rare bacteria that cause meningitis are not transmitted and, consistent with the tradeoff theory, the average bacterium in the population has low virulence. Thus, according to the tradeoff theory, meningitis can be viewed as a rare trait introduced at low frequency by mutation and kept at low frequency by selection against high virulence.

A second possibility is that meningitis is not caused by mutants, but simply by individuals of the normal bacterial population that happen to pass into the cerebrospinal fluid. On the one hand, this is evidence that an adaptive tradeoff theory cannot explain virulence. On the other hand, the adaptive tradeoff theory, like any theory based on general trends caused by natural selection, can only predict the average tendency in the population and not the details of rare cases. The average tendency of the bacterial populations that cause meningitis is low virulence.

Although the argument about meningitis is not settled, the tradeoff theory is useful because it provides a touchstone against which individual cases can be compared and alternative theories can compete. To provide a solid foundation, the theory itself must be developed and applied without ambiguity. This leads to the second problem for adaptive tradeoff theories—the theory itself is often misunderstood.

One commonly cited prediction from tradeoff theory is that the relative rates of horizontal and vertical transmission determine virulence. If a parasite is transmitted vertically, then parasite success is tied to the success of its host, and low virulence is favored. With horizontal transmission the parasite usually gains by exploiting the host to increase the rate of infectious transfer, leading to relatively high virulence. The horizontal versus vertical distinction is an appealing slogan that gives

a rough idea of how life histories may evolve in some cases. However, the mode of transmission does not inevitably influence virulence in even the simplest theories of parasite life history. I will justify this claim by working through the basic theory in the following sections.

After presenting the formal theory in the first third of this article, I summarize the main conclusions that are needed to apply the theory. On first reading, some may wish to skip ahead to the section "Summary of the theory" to prepare for the applications and discussion that follow. In the applications I criticize four recent studies in light of the conceptual framework developed in the theory section: Herre's (1993) analysis of nematode virulence in fig wasps; Ewald's (1994) models to explain extreme virulence in hospital epidemics; Ewald's (1994) theory that evolutionary pressures on virulence can be modified by changing the opportunity for horizontal transmission; and Levin and Bull's (1994) model of within-host evolution, as described in the meningitis example.

Each of these studies makes a significant contribution to the field. However, I will show that the basic tradeoff theory is applied in a misleading or incorrect way in each study. My criticisms are, in some cases, rather minor. But ambiguity in the conceptual foundations of a field will only lead to increasing confusion.

Transmission Versus Virulence

There are many different ways to describe the tradeoff between parasite transmission and virulence. The current standard for evolutionary models was developed by Anderson and May (1982). They showed that parasite fitness in a commonly used epidemiological model is

$$R_0 = \frac{\beta(\nu)N}{\delta + \nu + c(\nu)}, \qquad (1)$$

where δ is the host's disease-free mortality rate, ν is the disease-induced mortality rate (virulence), c is the rate at which hosts recover by clearing the infection, β is the transmission rate of disease upon contact between infected and susceptible hosts, and N is the total population size of the host. (I have changed the notation slightly from Anderson and May's usage.) The rates of clearance, $c(\nu)$, and transmission, $\beta(\nu)$, may depend on virulence, ν. These dependencies will be discussed below.

The terms in Equation (1) for R_0 have simple intuitive meanings. Transmission, $\beta(\nu)N$, is the number of new infections per unit time produced by one infected individual introduced into a population of N uninfected hosts. The denominator terms, $1/[\delta + \nu + c(\nu)]$, describe how long an infection is expected to remain within a host: the host may die of disease because of parasite virulence, ν, the infection may be cleared by the host, $c(\nu)$, or the host may die of other causes, δ. The product of transmission and residence time in the host determines the total number of new infections caused by an infected host; that is, the fitness of the parasite measured by number of "progeny" infections created.

From Equation (1) it is clear that higher transmission increases parasite fitness, whereas higher virulence decreases parasite fitness because it damages the parasites' food supply (the host). If transmission and virulence are coupled, then parasite fitness depends on a balance between the benefits of high transmission and the costs of increased virulence. Several recent models of virulence are derived from this equation for parasite fitness and the underlying epidemiological model. These models are discussed below.

The simple tradeoff between transmission and virulence can be seen more easily if we write parasite fitness, w, as

$$w = zf(z),$$

where z is proportional to transmission success, and $f(z)$ is a declining function of z (Frank 1994a). The function $f(z)$ represents traits such as virulence and clearance that reduce net fitness and are correlated with transmission, z. This is the same idea as Equation (1), but different forms of $zf(z)$ are often easier to work with when examining more complex genetical problems, as discussed below.

The simplest tradeoff occurs when an increase in transmission, z, causes a linear decline in the resources available from the host, $f(z) = 1 - \alpha z$. The parameter α is the scaling relation between transmission, z, and virulence, thus αz is the level of virulence. Re-

duced host resources are likely to be caused by morbidity or mortality from an increasingly virulent infection.

When there is only a single parasite clone in each host, then parasite fitness is optimized by finding the maximum of $w = zf(z)$ which, for $f(z) = 1 - \alpha z$, is given by $z^* = 1/(2\alpha)$. This is interesting because, at the maximum, the effect of virulence, αz, on fitness is $f(z^*) = (1 - \alpha z^*) = 1/2$ for any value of α. If we interpret $f(z)$ as the time period of infection, then selection favors infections that last 50 percent the length of an avirulent infection independently of α, the scaling (tradeoff) between transmission and virulence.

Another interesting point is that optimal fitness is $w^* = 1/(4\alpha)$, so that the parasites favor reducing their virulence effects, α, as much as possible. This is the so-called conventional wisdom, that parasites evolve to be benign toward their hosts (reviewed by Anderson and May 1991). But parasites do reproduce and transmit themselves by using host resources, so that there is inevitably a limit on reducing α, the tradeoff between virulence and transmission. This limit depends on the biology of each particular interaction.

Other functional forms can be used for $f(z)$, allowing one to study nonlinear relationships between transmission and virulence. For example, the functional forms for R_0 can be used and the same procedure followed (see below). This leads to qualitatively similar conclusions about the tradeoffs between transmission and virulence, although the quantitative details will always depend on specific assumptions.

Clearance Versus Virulence

Most studies have emphasized the tradeoff between transmission and virulence. But the simple model of R_0 in Equation (1) shows that a tradeoff between virulence and the rate at which hosts clear an infection can also influence parasite life history (Anderson and May 1982, 1991; Antia et al. 1994). For example, a parasite may have to replicate rapidly within the host to outpace the rate at which the immune system kills the parasites. Thus rapid parasite multiplication and parasite virulence may be caused by selective pressures on the parasite imposed by the immune system. As Antia et al. (1994) put it, the immune system may impose a selective force that favors virulence in those parasites that it controls and clears.

The simplest model of clearance versus virulence follows directly from the equation for R_0 (Anderson and May 1982; Levin 1983; Frank 1992). We can write parasite fitness as $w = zf(\nu)$, where z is the number of secondary infections per unit time (transmission) and $f(\nu)$ is the expected time that an infection survives in a host. Here the level of virulence, ν, is favored to maximize the expected survival time in a host, $f(\nu)$. From Equation (1),

$$f(\nu) = 1/[\delta + \nu + c(\nu)],$$

and a simple way to describe the tradeoff between virulence and clearance is $c(\nu) = \gamma/\nu^\tau$, where γ and τ are parameters that determine the shape of the tradeoff. The predicted virulence is obtained from maximizing $f(\nu)$ with respect to ν, yielding

$$\nu^* = (\gamma\tau)^{1/(\tau+1)}. \qquad (2)$$

This model assumes that only one parasite genotype infects each host. When there are multiple infections, competition within hosts must be taken into account. Multiple infection is discussed in the following sections, and an extension of Equation (2) is given, along with a graph showing how particular parameters influence the tradeoff between clearance and virulence (see below).

Ecological and Evolutionary Processes

Before turning to models of multiple infection we must face a difficulty with the theory. Realistic models should account for the complex interactions between ecological and evolutionary processes, yet simpler models that isolate and analyse a few key processes have not been fully worked out. I briefly introduce the problem by discussing superinfection.

The bacteriophage lambda prevents new infections when it integrates into the host genome and is transmitted vertically (Lewin 1977). In other host-parasite systems the parasites may superinfect and "take over" a host by driving out the resident genotype, although I do not know of a well-documented case.

The theoretical consequences of superinfection are complex (May and Nowak 1994; Nowak and May 1994). There is an evolutionary

component of competing genotypes with different characteristics for virulence, transmission, and competitiveness within hosts. There is also an ecological (epidemiological) component of the numbers of uninfected and infected hosts available to the parasites and the ease with which a parasite can succeed in primary infection versus superinfection. The evolution of transmission and virulence will feed back on the ecological component of the numbers of uninfected and infected hosts, which in turn influences the evolutionary success of different genotypes, and so on.

One approach is to combine ecological and evolutionary processes into a single model. But beginning with too many processes often yields complex outcomes that are difficult to understand. The model is neither sufficiently simple to isolate and explain one or two key factors nor sufficiently complex to be a realistic description for any host-parasite system.

I will first describe simple models that isolate key processes. This reductionistic approach is useful as long as one does not lose sight of the ultimate goal—combining ecological and evolutionary factors into a realistic description of virulence evolution. In later sections I will return to the problem of combining different processes.

Multiple Infection and Mutation

Kin Selection and Group Selection

Genetic variation of parasites within hosts often favors increased virulence (Hamilton 1972; Bremermann and Pickering 1983; Knolle 1989; Sasaki and Iwasa 1991; Nowak and May 1994). I first present a simple example to show how higher virulence can be favored. This example demonstrates that the evolution of virulence with multiple parasite strains per host is a typical problem for the theory of kin selection and group selection (Frank 1992, 1994a; van Baalen and Sabelis 1995). I then provide a more general model to show the processes that influence virulence, including tradeoffs with transmission and clearance.

A simple tradeoff between transmission and virulence was given above in the equation $w = z(1 - \alpha z)$. Here z is transmission and αz is virulence. This fitness function assumes that there is only one parasite genotype per host. We can extend this equation for multiple infection by focusing on a parasite strain, a, and labeling all other strains b. The hosts in the population are labeled by $i = 1, \ldots, N$. The fitness of the a genotype in the ith host is

$$w_{ia} = z_{ia}(1 - \alpha z_i) ,$$

where $z_i = q_{ia}z_{ia} + q_{ib}z_{ib}$ is the average value of z in the ith host. The q's are the frequencies of the parasite genotypes a and b within the ith host.

We could proceed to analyse this equation, but first let us consider the biological assumptions implied by this expression for fitness. As before, the form $zf(z)$ describes a tradeoff between transmission and virulence. However, this new formulation assumes that the multiple genotypes per host affect these two fitness components differently. The genotype directly and independently controls its own transmission rate, z_{ia} without competition or influence from the other genotypes. By contrast, virulence effects are a weighted average of the different genotype effects in the host, αz_i. These different effects make sense in some cases (see below, "Mechanisms of transmission and clearance"), but often multiple parasite genotypes compete for limited host resources or opportunities for transmission. For example, if vectors transmit a fixed volume of blood, and genotypic success depends on relative frequency in the vector, then the transmission success of genotype a from the ith host is z_{ia}/z_i.

Within-host competition for resources and transmission combined with virulence is thus described most simply by

$$w_{ia} = (z_{ia}/z_i)(1 - \alpha z_i) . \qquad (3)$$

The term (z_{ia}/z_i) is selection within hosts. The second component, $(1 - \alpha z_i)$, describes selection among hosts. For example, if this component is the duration of infection before the host dies, then the total group fitness of parasites within the host will, in this model, increase as z decreases. The most productive groups of parasites within hosts are those that cause the least damage to the host. The full fitness function combines selection within groups (hosts) and selection among groups. Selection within hosts favors rapid growth (high z); se-

lection among hosts favors reduced growth rate (low z).

The combined effects of selection within and among hosts can be seen by first considering two extreme cases. In the first case, there is only one parasite genotype in each host, thus there is no selection within hosts. This example isolates the effects of selection among hosts. For example, if a host contains only genotype a, then $z_i = z_{ia}$ and

$$w_{ia} = (z_{ia}/z_{ia})(1 - \alpha z_{ia}) = (1 - \alpha z_{ia}) .$$

Thus parasite genotype a, when alone, maximizes its fitness by being nearly avirulent, $z_{ia} \to 0$, where the arrow means "close to zero." Selection favors low virulence when acting only on variation in the productivity of parasites living in different hosts.

In the second case there are equal numbers of genotype a and b in every host. Because all hosts have the same composition of parasites, the same selective dynamics occur within each host. Thus the direction of evolutionary change within hosts will be the same as the direction of evolutionary change in the entire population. The within-host component of fitness for genotype a is z_{ia}/z_i, which increases with increasing z_{ia}. Within-host selection thus favors maximal reproductive rate and competition among parasite strains. However, pure within-host selection, with no counterbalancing pressure from selection among hosts, is very unlikely because it requires that genotypic composition be exactly the same in all hosts with no variation among hosts.

The next step is to combine within-host selection and among-host (group) selection (Levin and Pimental 1981). There is much literature on this subject and many theoretical methods (Wade 1978; Wilson 1980; Grafen 1984; Queller 1992). I will introduce a simple method here.

A potential equilibrium phenotype for the character z can be obtained by maximizing w_{ia} in Equation (3) with respect to z_{ia} (Maynard Smith 1982). This is a valid method if we assume that the alleles controlling z have additive effect. The technique is to take the derivative of Equation (3) with respect to z_{ia}, set the result to zero, set $z_{ia} = z_{ib} = z^*$, and solve for z^*. This is just a trick for finding a value of z^* such that any phenotype deviating slightly from this optimum has lower fitness. Following through yields $\alpha z^* = 1 - dz_i/dz_{ia}$, where dz_i/dz_{ia} is the derivative of z_i with respect to z_{ia}, i.e., the slope of the average genotype within host i relative to individual genotype. The slope of group genotype on individual genotype is the coefficient of relatedness from kin selection theory (Hamilton 1972). Thus we obtain the equilibrium level of virulence by replacing dz_i/dz_{ia} with r, the coefficient of relatedness (Taylor and Frank In press), yielding

$$\alpha z^* = 1 - r . \qquad (4)$$

The coefficient of relatedness is simply a measure of statistical correlation or association. If $r = 1$, then individual and group genotype are identical and there is no variation within groups. If there are n separate infections of a host, each by a parasite genotype randomly chosen from the population, then the relatedness of parasites within hosts is $r = 1/n$. In this case the association between the value of each genotype and the group average, $1/n$, is caused by the fact that each individual is perfectly correlated with itself and uncorrelated with the other $n - 1$ individuals in the group. Other patterns of correlation are described just as easily. For example, if each individual is correlated with the other $n - 1$ group members by 1/2, then $r = [1 + (n - 1)/2]/n = (n + 1)/2n$.

This kin selection model describes statistical aspects of variation by measuring association within groups. Sometimes it is useful to highlight the complement measure, the genetic variation among groups, which emphasizes that there is a form of group selection occurring. The relationship between kin and group selection models is very simple: the variation among groups is $1 - r$. Statistical association within groups, r, and statistical variation among groups, $1 - r$, are alternative ways of saying the same thing. Although the point is trivial, the two descriptions of variation are sometimes mistakenly discussed as if they led to two distinct processes. The descriptions can be used interchangeably, but one or the other may be better when extending the model in particular ways. For example, I will use the group selection description when discussing nonequilibrium dynamics in order to emphasize the opposing directions of evolu-

tionary change favored by within-group and among-group selection (see below).

PREDICTIONS FOR VIRULENCE

The result in Equation (4) shows that selection favors increased virulence when relatedness declines among coinfecting parasites. Put another way, the cooperative and prudent exploitation of the host, with low virulence and long residence time, depends on a high degree of genetic relatedness among the parasites. This assumes, of course, that there is in fact a tradeoff between virulence and either transmission or clearance. In this section I discuss the quantitative relationships among genetic variability and virulence under the assumption that such tradeoffs exist. In the following section I consider how the actual mechanisms of transmission and clearance can change the predicted relationship between genetic variation and virulence.

Three processes influence the genetic variability of parasites within hosts (Frank 1994a): Mutation increases genetic variability (Bonhoeffer and Nowak 1994a); sampling (segregation) of parasites during transmission reduces genetic variability because only a subset of parasites are transmitted from one host to the next; and multiple infection increases variability by mixing different parasite strains within hosts (Bremermann and Pickering 1983). I will discuss these processes more explicitly in the following paragraphs. In each case, the simple result in Equation (4) shows how genetic variability affects virulence. It must be remembered that the genetic variability that matters is in the trait z, which affects transmission and virulence by influencing the parasites' reproductive rate and the damage to the host.

The first example focuses on mutation and segregation, with only a single infection per host. There are two ways of thinking about this situation. In the first scenario, obligate parasites (symbionts) are transmitted vertically through the cytoplasm. There is no mixing because inheritance is uniparental. Thus genetic variability is influenced only by mutation, the sampling (segregation) of the parasites to be transmitted to the next generation, and selection. Mitochondria and many obligate bacterial and viral symbionts fit this pattern.

In the second scenario, parasites are transmitted horizontally among hosts. Each host is infected only once, with all parasites derived from the same donor host. Thus genetic variability is influenced only by mutation, the segregation of the parasites to be transmitted to the next host, and selection.

This example also describes a mixture of horizontal and vertical transmission as long as parasite lineages do not mix. In each case segregation occurs when k parasites are chosen for transmission from the pool of parasites within the donor host. These two scenarios of vertical and horizontal transmission are identical with respect to the way genetic variability and kin selection influence the evolution of virulence. Ecological aspects of horizontal and vertical transmission are discussed later.

Mutation, segregation and selection combine to determine the equilibrium level of virulence, as shown in Figure 1. In that figure, $\alpha = 1$ and the equilibrium virulence is $z^* = 1 - r$, as in Equation (4). The relatedness coefficient, r, is determined by mutation and segregation. As expected, the figure shows that increased mutation increases virulence, z^*, and, because $r = 1 - z^*$, increased mutation also decreases relatedness. Larger samples during segregation, increased k, decrease relatedness because there are more individuals founding a new group within a host. Lower relatedness leads to increased virulence.

This simple model can be extended to emphasize how parasite traits cause correlations among different components of fitness. Let the single parasite trait z affect virulence and competitiveness at different, correlated rates: virulence is αz and competitiveness within the host is λz. Thus the ratio of virulence to competitiveness is α/λ. The new model is

$$w_{ia} = [(1 - \lambda) + \lambda z_{ia}/z_i](1 - \alpha z_i), \quad (5)$$

with equilibrium virulence

$$\alpha z^* = \frac{\lambda(1 - r)}{\lambda(1 - r) + r}. \quad (6)$$

I will use this extended model as the basis for further modifications.

The previous case analysed mutation and segregation. The next example focuses on multiple infection, which can also be thought of as migration between groups of parasites.

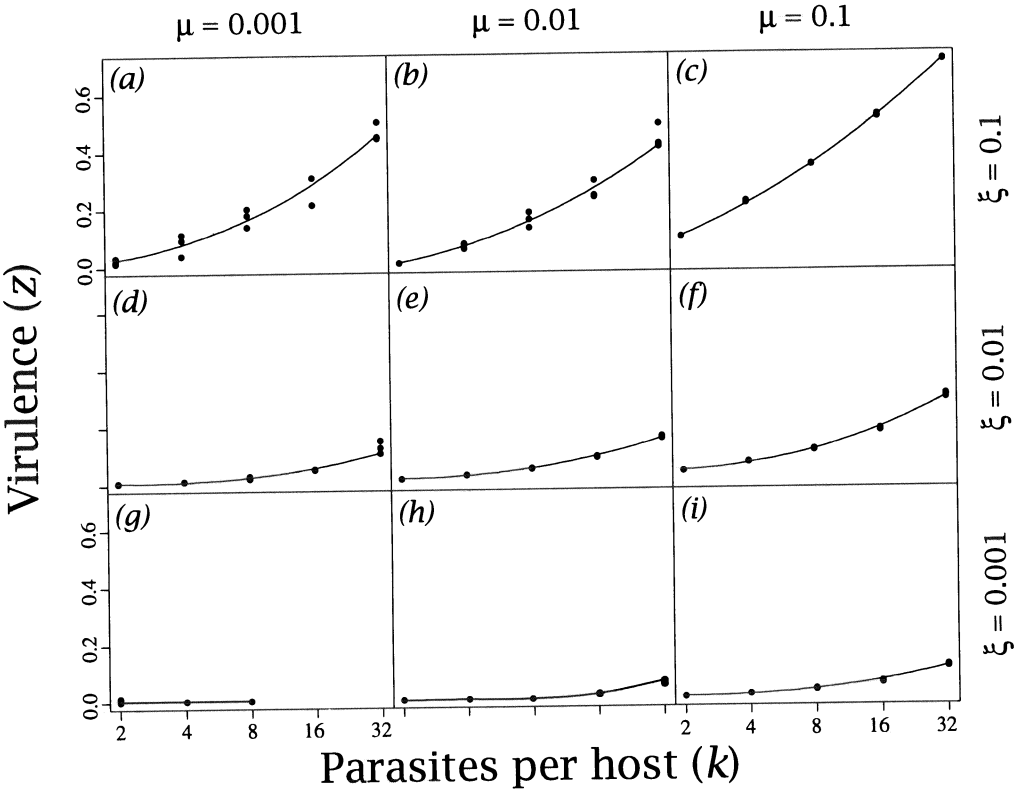

FIGURE 1. THE EQUILIBRIUM LEVEL OF VIRULENCE IN A MODEL WITH VERTICAL TRANSMISSION AND NO MIXING

Virulence, z, is determined by the number of parasites per host, k, the mutation rate, μ, and the effect per mutation, ξ. The equilibrium virulence closely matches the prediction $z^* = 1 - r$ as discussed in the text, where relatedness, r, is determined by a balance among mutation, selection and segregation. The plots show data from a simulation. In each run a population of 1000 hosts was initialized with k parasites, each with a trait value that was chosen according to a uniform random number between 0 and 1. In each generation 1000 hosts were selected stochastically for reproduction with probabilities proportional to host fitness $1 - z_i$, where z_i is the average trait value of parasites in the ith host. For each host chosen, k replicates of parasites were chosen stochastically from the parasite pool. A replicate of a parasite was chosen (with replacement) with probability proportional to relative fitness within the host, z_{ij}/z_i, where z_{ij} is the trait value of the jth parasite in the ith host. Progeny parasites mutate at rate μ, with each mutation causing a change in trait values by an amount $\pm\xi$. The simulation was run for 15,000 generations to initialize the system, and then the average trait value in the population, $\bar{z}$, and the coefficient of relatedness between pairs of parasites within hosts, r, were measured in the following 15,000 generations. The plots show the median value of $\bar{z}$ over 15,000 generations for each of three replicate runs and for each combination of parameters k, μ and ξ. In panels (g) and (h) I used a population size of 10,000 and 45,000 generations of initialization because drift is stronger and convergence is slower for weak mutational effects. In panel (g) close convergence to equilibrium (of order 10^{-3}) required 150,000 generations of initialization for the case of $k = 8$. Constraints on computer time prevented runs for $k = 16,32$ for this panel. Further details are in Frank (1994a).

Multiple infection is dealt with in the following way. For each new host, the probability that two infecting parasites come from the same donor host is $1 - m$, and, with probability m, infecting parasites are chosen randomly from the population. Thus m is the migration

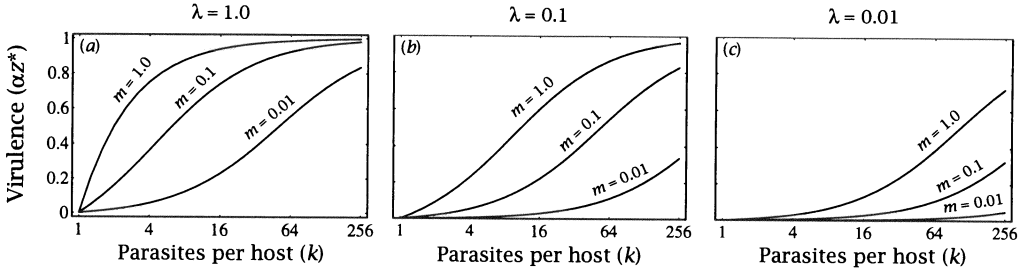

FIGURE 2. EVOLUTION OF VIRULENCE
Virulence is controlled by the number of parasites per host, k, and the rate of passive migration, m. The parameter λ controls the strength of association between virulence and competitiveness.

rate into each lineage of parasites. The total number of parasites infecting a host is k. Increases in k decrease relatedness (genetic similarity) within hosts.

If we assume the parasites are haploid, then the coefficient of relatedness r is calculated in the same way as the standard inbreeding coefficient of population genetics, F. Using the assumptions about migration and segregation, the change of F over time is

$$F' = (1/k) + F[(k - 1)/k](1 - m)^2 . \quad (7)$$

The equilibrium can be obtained by setting $F' = F$, where F' is the value of F after one round of segregation and migration at rate m (see Appendix). The equilibrium is

$$r = F = 1/[k - (k - 1)(1 - m)^2] , \quad (8)$$

which allows the equilibrium virulence, αz^* in Equation (6) to be expressed in terms of the number of parasites per host, k, the amount of mixing between groups of parasites, m, and the rate λ at which changes in the parasite trait, z, affect competitiveness within the host. The prediction is shown in Figure 2a. Other patterns of mixing would lead to different recursions for F, but the method of solution would be the same.

These results for relatedness depend on the linear tradeoffs given by the fitness function in Equation (5). But this equation was chosen arbitrarily for its simplicity. Most studies of parasite epidemiology and virulence use a fitness function such as R_0 in Equation (1) that has been derived from specific epidemiological equations for the dynamics of disease. In the remainder of this section I use that equation for R_0 as the fitness function to show that the nonlinear tradeoffs in R_0 alter the quantitative details of the results, but still show the fundamental role of relatedness among parasites in determining virulence. I then look at the tradeoff between clearance and virulence when there is genetic variation among parasites within hosts.

The fitness function R_0 written in the notation we have been using to label genetic variation within and among hosts is

$$w_{ia} = \beta(v_{ia})N/[\delta + v_i + c(v_{ia})] , \quad (9)$$

where v_{ia} is the virulence phenotype of parasite genotype a in host i, and v_i is the average virulence of parasites in host i. I assume here that the transmission rate of a genotype depends only on its own phenotype, v_{ia}, and does not depend on the genotypic composition of parasites within the host. Similarly, the rate of clearance of a genotype depends only on its own phenotype and not on the phenotype of other parasites in the host. These assumptions are relaxed in the next section.

The method needed to obtain the predicted equilibrium virulence from Equation (9) is the same as used to obtain Equation (4), but the nonlinearities in Equation (9) make the process more tedious. Taking the derivative of Equation (9) with respect to v_{ia}, evaluated at the equilibrium $v^* = v_{ia} = v_{ib}$, yields

$$\frac{d\beta(v)}{dv}(\delta + v^* + c(v^*)) - \beta(v^*)\left(r + \frac{dc(v)}{dv}\right) = 0, \quad (10)$$

where the derivatives with respect to v are evaluated at v^* (Frank 1992). This equation

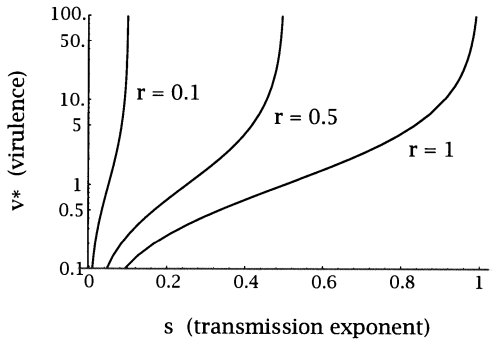

FIGURE 3. PREDICTED LEVEL OF VIRULENCE
Virulence (v^*) is a function of relatedness, r, and the exponent s in the relationship between transmission and virulence, $\beta(v) = bv^s$. The figure is based on Equation (12) with $\delta + \gamma = 1$ (Frank 1992).

shows that the equilibrium depends on relatedness, r, the slope (tradeoff) between transmission and virulence, $d\beta(v)/dv$, and the slope between clearance and virulence, $dc(v)/dv$. Specific functional forms for β and c are useful for analysing the equilibrium in Equation (10):

$$\beta(v) = bv^s$$
$$c(v) = \gamma/v^\tau \quad . \tag{11}$$

Transmission, β, increases with increasing virulence, v, and clearance, c, decreases with increasing virulence.

If the only tradeoff is between transmission and virulence, $\tau = 0$, then

$$v^* = \frac{s(\delta + \gamma)}{r - s} \qquad r > s$$
$$\to \infty \qquad r \le s \,, \tag{12}$$

which is a generalization of the formula given by Bremermann and Pickering (1983) for single-strain infections in which $r = 1$. Equation (12) shows the quantitative relationships among relatedness of coinfecting strains, r, the rate of change in transmission with virulence, s, and the expected patterns of virulence evolution, v^* (Figure 3). Note in Equation (12) that virulence is favored to be as large as possible when $s > r$. This result is a generalization of Anderson and May's (1982) comment that, for the special case of one strain per infection, $r = 1$, large virulence is favored when transmission increases at a greater than linear rate with increasing virulence, $s > 1$.

If the only tradeoff is between recovery rate and virulence, $s = 0$, then

$$v^* = \left(\frac{\gamma\tau}{r}\right)^{1/(\tau+1)} \quad . \tag{13}$$

This tradeoff has a strongly stabilizing effect on virulence (Figure 4), as noted by Anderson and May (1982, 1991) and by Antia et al. (1994). The equilibrium virulence increases with declining relatedness within each host (Frank 1992). With lower relatedness, there is greater within-host selection favoring rapid reproduction by the parasites to delay clearance. The individual benefits of within-host selection and delayed clearance are balanced by the group-selected costs of damaging the host more severely or more quickly because of higher virulence.

MECHANISMS OF TRANSMISSION AND CLEARANCE

The results for tradeoffs between transmission and virulence depend on the assumption that transmission is a property of each genotype in a mixed infection rather than of the aggregate genotype (Frank 1992). If, however, transmission increased with the number of lesions formed, and each genotype gained equally from each lesion, then transmission would be a property of the aggregate. Because the transmission rate of each genotype depends on the average genotype in the host, the term $\beta(v_{ia})$ would be replaced by $\beta(v_i)$ in Equation (9). Following through, the solution would be obtained by setting $r = 1$ in Equation (12). In this case there would be no conflict among parasite strains within a host, and the evolution of virulence would be independent of the relatedness among coinfecting strains.

The results above for tradeoffs between clearance and virulence also depend on the distinction between individual and group properties. If, for example, the host immune response acts indiscriminately against the different parasite strains, then the host clearance term depends on aggregate genotype. In this case the term $c(v_{ia})$ would be replaced by $c(v_i)$ in Equation (9) and, following through, the solution would be obtained by setting $r = 1$

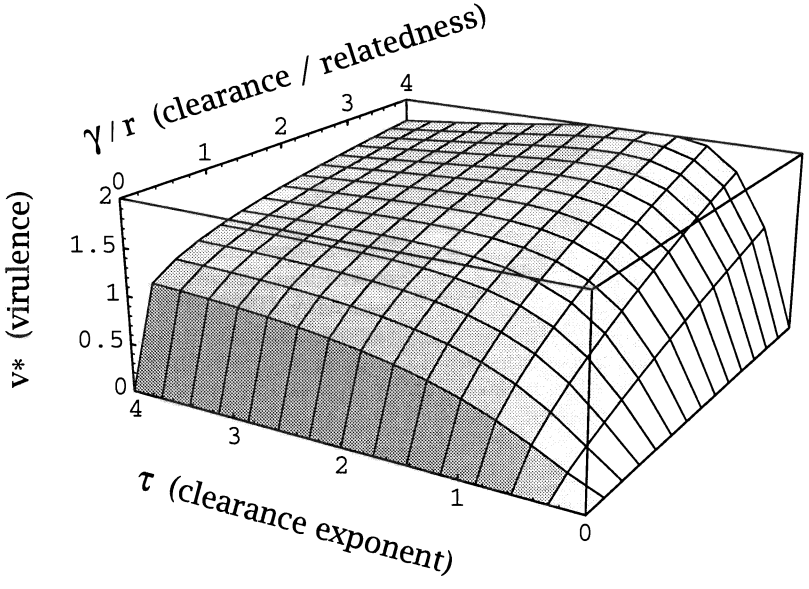

FIGURE 4. PREDICTED LEVEL OF VIRULENCE
The tradeoff between virulence and recovery (clearance) rate given by $c(v) = \gamma/v^{\tau}$. The figure is based on Equation (13) (Frank 1992).

in Equation (13). As in the transmission case, dependence only on the aggregate genotype removes the conflict among strains and reduces the predicted level of virulence in multiple infections.

The important point here is that the models cannot be applied without careful consideration of the biology of particular host-parasite interactions. For example, Bonhoeffer and Nowak (1994b) presented an interesting discussion of how different viruses interact with the host immune system. Adenoviruses have several mechanisms that obstruct T-cell recognition and destruction of infected cells. These mechanisms act locally, within or on the surface of infected cells, so that only the individual viruses expressing these mechanisms gain by reducing their rate of clearance. By contrast, poxviruses have several mechanisms that interfere with nonspecific systems of host defense. A virus gains whenever these extracellular defenses are blocked, whether or not the virus itself produces the antihost compounds.

In the above models, each individual adenovirus affects its own clearance rate, so $c(v_{ia})$ is the appropriate term and virulence increases as relatedness declines. Traits of the poxvirus affect the clearance of all viruses, so $c(v_i)$ is the appropriate term for these pathogens, and virulence is independent of relatedness. Bonhoeffer and Nowak (1994b) provide a similar interpretation for intrahost and interhost selection, which is another way of describing kin and group selection processes.

Mechanisms of transmission may also require careful attention. For example, the total transmission from a host may be fixed by the vector. If mosquito-borne transmission is independent of the concentration of circulating pathogens when above a small threshold concentration, then transmission for the group of pathogens within the host is fixed. If proportional representation in the blood meal is directly related to transmission, then transmission of a genotype depends on relative competitiveness within the host, for example, z_{ia}/z_i in Equation (3). Alternatively, if each pathogen's transmission rate depends only on its own concentration in the blood, then one could use the transmission term $\beta(v_{ia})$ from Equation (9). Again, the main point is that

some care is required when applying models to particular cases.

SELECTION OF PARASITE DISPERSAL RATES

In the previous sections I examined the evolution of competitiveness and virulence as correlated characters determined by a single underlying trait, z. Competitiveness for resources within the host determines each parasite's success relative to its neighbors. Damage to the host's health (virulence) determines the average success of the group of parasites within the host, because the parasites live within the host and their total success is tied to the vigor of the group. I now add the third key characteristic of a parasite, the transmission (migration) from one host to another. The evolution of characters influencing transmission is added to the model by allowing the rate of migration to be under genotypic control (Frank 1994a).

I introduce the problem by reviewing a standard model for the evolution of dispersal when relatives compete for local resources (Hamilton and May 1977; Motro 1982; Frank 1986; Taylor 1988). The particular model and the results that I summarize are explained in Frank (1986).

The fitness function for a trait z_{ia} that determines the dispersal rate for parasite genotype a in the ith host is

$$w_{ia} = \frac{(1 - z_{ia})}{1 - z_i + (1 - c)\bar{z}} + \frac{(1 - c)z_{ia}}{1 - \bar{z} + (1 - c)\bar{z}}. \quad (14)$$

The first term is, in the numerator, the success of an individual that stays at home with probability $1 - z_{ia}$ relative to, in the denominator, the intensity of competition at home given by the frequency of nonmigrants, $1 - z_i$, plus the frequency of immigrants, $(1 - c)\bar{z}$, where $\bar{z}$ is the average rate of dispersal and c is the mortality (cost) incurred during dispersal. The second term is, in the numerator, the success of an individual that migrates with probability z_{ia} and survives the journey with probability $1 - c$. Upon arrival it faces competition from nonmigrants with, in the denominator, frequency $1 - \bar{z}$, and from other immigrants that arrive at a frequency of $(1 - c)\bar{z}$.

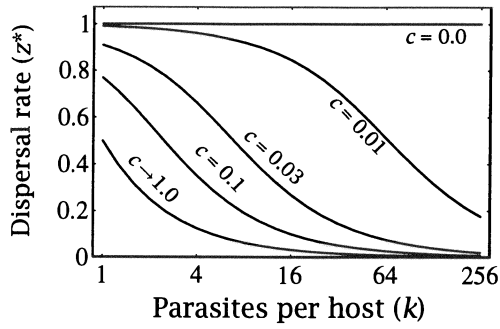

FIGURE 5. EVOLUTION OF DISPERSAL RATE
Dispersal rate (z^*) is controlled by the number of parasites per host (k) and the cost of dispersal, (c).

The method outlined above can be used to obtain the equilibrium dispersal rate

$$z^* = \frac{r - c}{r - c^2}, \quad (15)$$

where r is the coefficient of relatedness among parasites within hosts, and c is the cost of dispersal. We can use Equation (8) for the equilibrium value of r, but now the migration rate m in that equation depends on dispersal, z. The rate of successful migration is $m = (1 - c)\bar{z}/(1 - c\bar{z})$. Substituting this value of m into Equation (8) to obtain r, and then using that value of r in Equation (15), we obtain a nonlinear equation in z^* that can be solved numerically for the equilibrium dispersal rate in terms of the cost of migration, c, and the number of parasites per host, k (Taylor 1988). The result is plotted in Figure 5. This result holds unless mutational effects are of greater magnitude than the rate of successful migration, m. When mutation is sufficiently strong relative to migration, relatedness is reduced and the rate of dispersal declines.

In summary, competition among relatives within hosts favors the evolution of increased horizontal transmission. This increased "dispersal" may occur by enhanced mixing among sets of parasites during transmission or by additional release of propagules from a stable host.

COMBINING COMPETITIVENESS, DISPERSAL AND VIRULENCE

I now incorporate the evolution of migration (parasite transmission) as a correlated trait of competitiveness and virulence. There

are several ways in which correlations can arise among these traits. For example, dispersal may require more resources, such as a protein coat. Thus, dispersing parasites may use resources more quickly than nondispersers, increasing competitiveness and reducing the vigor of the group. Lower group success is synonymous with virulence in these models.

I assume that there is an underlying parasite trait z such that competitiveness, virulence and dispersal probabilities are λz, αz and dz, respectively. These traits are combined into a fitness function by merging Equation (5) and Equation (14) to yield

$$w_{ia} = \left((1 - \lambda) + \lambda\left(\frac{z_{ia}}{z_i}\right)\right)(1 - \alpha z_i) \times \left(\frac{(1 - dz_{ia})}{1 - dz_i + (1 - c)d\bar{z}} + \frac{(1 - c)dz_{ia}}{1 - d\bar{z} + (1 - c)d\bar{z}}\right).$$

This model emphasizes the extent to which selection on each character affects the evolution of the other characters.

This equation contains the previous models as special cases. For example, if $d = 0$, then one obtains Equation (5) and the equilibrium result in Equation (6). If $\lambda = \alpha = 0$, then the equilibrium dispersal probability dz is given by the result for z^* in Equation (15).

The equilibrium for the full model is obtained with the methods described above. The result is a long polynomial in z^*, not shown here (see Frank 1994a for details), that can be evaluated with standard numerical methods.

The equilibrium trait value, z^*, depends on five parameters. The parameters λ, α, and d determine the relationship between the trait, z, and competitiveness, virulence and dispersal, respectively. The parameters k and c are the number of parasites per host and the cost of dispersal. Results for various parameter combinations are shown in Figure 6 and discussed below.

SUMMARY OF KIN SELECTION MODELS

Kin selection plays a central role in the evolution of parasite life history. The first model analysed a simple tradeoff between competitiveness within the host and virulence, Equation (3). The formal result for this model is $z^* = 1 - r$; virulence depends on one minus the relatedness among parasites within hosts. This result isolates an important process that occurs in a variety of more complex models (Bremermann and Pickering 1983; Frank 1992, 1994a; Nowak and May 1994). The model also matches the intuitive notion that increased relatedness within hosts decreased competition, thus reducing harm to the host and increasing the success of the local group of parasites.

The analysis showed an interesting distinction between life cycles in which relatedness is dominated by mutational processes and those in which migration dominates. When mutation is more potent than migration, relatedness and virulence are held in a delicate balance among mutation, selection and segregation (Figure 1). For example, mutation is the only factor in a vertical, uniparentally inherited parasite. In this case, the number of parasites k sampled in each generation can greatly influence relatedness and virulence. Small k increases the sampling variance among hosts and thus increases relatedness, which enhances cooperation and reduces virulence. Virulence rises with increasing k.

The second model applied a theory of dispersal based on kin selection to the evolution of parasite transmission rates. Previous theory showed that dispersal rates increase as the relatedness rises among competitors within a natal patch (Hamilton and May 1977). The surprising outcome is that dispersal rates can rise to high levels even when the probability of successful migration is low (high cost, c, in Figure 5). The reason is that an individual competing with close relatives gains little net inclusive fitness by winning locally against its relatives. Even a small chance of successful migration to compete against nonrelatives can favor high dispersal rates.

In terms of parasite life history, increased relatedness within the host favors traits that enhance horizontal transmission. Selection favoring enhanced transmission can occur even if the rate of successful transmission is low. There is a subtle feedback in this process. If successful transmission is rare (high cost, c), then relatedness within hosts is likely to be high, which in turn favors traits that enhance

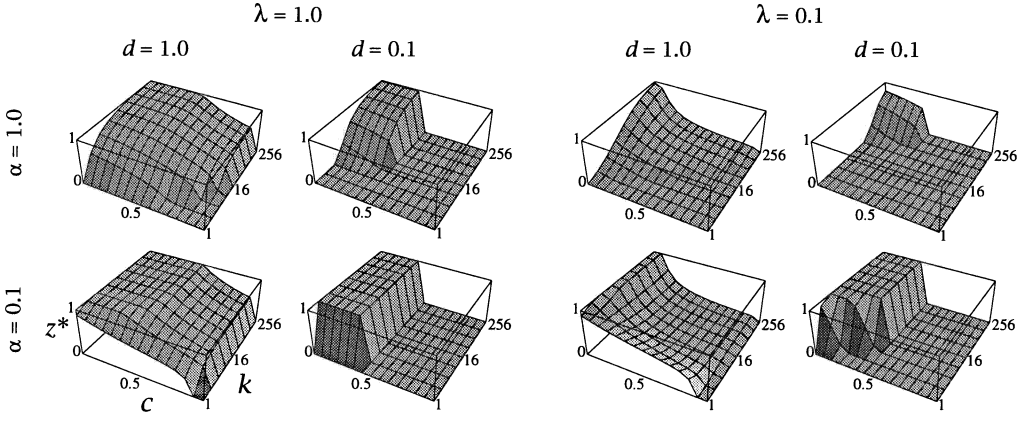

FIGURE 6. EQUILIBRIUM TRAIT VALUES z^*

Trait value z affects three correlated characters: virulence is αz, competitiveness with hosts is λz, and the active dispersal rate is dz. Each plot shows z^* as a function of the number of parasites per host, k, and the cost of dispersal, c (Frank 1994a).

transmission. However, to complete this analysis it is necessary to consider another type of cost for parasite dispersal: the mechanisms of horizontal transmission often have virulence effects on the host (e.g., diarrhea).

The final model ties together the traits of competitiveness, virulence and dispersal. I assumed that each of these three traits changed linearly with a single underlying cause, z. I varied the rate of change for each trait in order to study how correlations among these traits influence the evolution of parasite life histories. The results are shown in Figure 6. The equilibrium levels of competitiveness, virulence and dispersal are λz^*, αz^* and dz^*, respectively. The probability of successful migration is $1 - c$, where c is the cost of dispersal. The number of parasites infecting each host is k.

Reducing the effects of virulence, α, causes an increase in both dispersal rate and competitiveness within the host (compare the top and bottom rows of panels in Figure 6). The change in α for the case $\lambda = 0.1$ and $d = 1.0$ is particularly interesting. With strong virulence effects ($\alpha = 1.0$), high dispersal and competitiveness occur only when the costs of dispersal are low and the number of parasites per host is high. In this case relatedness among parasites in each host is low and, as expected, competition among parasites drives the evolution of trait values. The drop with increasing cost of dispersal at high k appears to be a more complex effect. The most likely explanation is that high costs of dispersal cause low rates of successful migration and high levels of relatedness in hosts. This in turn reduces the strength of selection on competitiveness, thus lowering the equilibrium trait values.

With low virulence effects, $\alpha = 0.1$, for $\lambda = 0.1$ and $d = 1.0$, competitiveness (λz) and dispersal (dz) are nearly unchanged or else rising as k declines. A drop in k causes increased relatedness within hosts. In this case selection on transmission rates appears to be driving the evolution of parasite life histories because competitiveness within a host increases despite the rise in relatedness among competitors. Interactions among the five parameters and the dynamics of relatedness determine the parasite life histories shown in the other panels of Figure 6.

I assumed that the three traits, competitiveness, virulence and dispersal, were all controlled by a single underlying cause. In reality there may be a number causes for the correlations among traits. My simple model describes the main tradeoffs but cannot provide a complete analysis without adding many more parameters. It is reasonable to assume that such tradeoffs may occur, but difficult to envision the specific mechanisms. The model empha-

sizes the general processes that must always be present whenever tradeoffs occur.

Nonequilibrium Models of Parasite Virulence

The previous models focus on equilibrium virulence for diseases that are at a stable, endemic frequency. In this section I consider two aspects of dynamics. First, I show that the evolutionary forces shaping virulence differ for endemic diseases and epidemic diseases that are spreading in a population. Second, I describe how the evolutionary dynamics of parasites within hosts can maintain a low frequency of extremely virulent disease. These virulent cases can occur in parasite populations that are typically benign.

DYNAMICS OF EPIDEMICS

In a previous section I discussed a commonly used measure of parasite fitness

$$R_0 = \frac{\beta(\nu)N}{\delta + \nu + c(\nu)}, \qquad (16)$$

where δ is the host's disease-free mortality rate, ν is the disease-induced mortality rate (virulence), c is the rate at which hosts recover by clearing the infection, β is the transmission rate of disease upon contact between infected and susceptible hosts, and N is the total population size of the host. The rates of clearance, $c(\nu)$, and transmission, $\beta(\nu)$, may depend on virulence, ν.

R_0 is the number of secondary (progeny) infections caused by a single infected individual introduced into an uninfected population (Dietz 1975, 1976; Yorke et al. 1979; Anderson and May 1981). For some simple models (e.g., no superinfection, no vertical transmission) Bremermann and Thieme (1989) showed that the genotype with highest R_0 will be favored by selection. However, R_0 is a legitimate measure of parasite fitness only when the host-parasite system is at equilibrium (Lenski and May 1994; Bull 1994; Lipsitch and Nowak 1995). For example, suppose that one parasite strain has transmission and virulence properties that cause it to produce two secondary infections per day and to have an average lifetime in a host of one day, so that $R_0 = 2$. Another strain produces one secondary infection per day and has an average lifetime in a host of five days, so that $R_0 = 5$.

Which strain has higher fitness? If the host-parasite system is at equilibrium, then the strain with higher R_0 wins. In some situations, however, epidemics rarely come to equilibrium, so we have to consider the dynamics of infection. For example, if two parasite strains are rare and spreading through a population, then the strain with the higher rate of increase (birth rate minus death rate) will spread more quickly. For the strains mentioned above, the one with $R_0 = 2$ has birth minus death rate of $2 - 1 = 1$, and the one with $R_0 = 5$ has birth minus death rate of $1 - 0.2 = 0.8$. The strain with $R_0 = 2$ has the higher rate of increase and thus spreads more quickly.

Analysis of a dynamical model will help to clarify how selection shapes virulence in endemic and epidemic conditions. A simple, commonly used dynamical model is

$$\begin{aligned} dx/dt &= \theta - \delta x - \beta xy \\ dy/dt &= y(\beta x - \delta - \nu - c), \end{aligned} \qquad (17)$$

where the terms are the same as in Equation (16), and x is the number of uninfected hosts, y is the number of infected hosts, and θ is a constant rate of immigration of uninfected hosts (Anderson and May 1991). This immigration rate is a simple way of maintaining a constant host population in the absence of infection. Each infected individual causes βx new infections, where βx is the transmission rate times the number of susceptible hosts. The rate at which infections are ended by natural host death, virulent death, or clearance, is $(\delta + \nu + c)$, so that the average lifetime of an infection in a host is $1/(\delta + \nu + c)$. Thus the number of secondary infections caused by each infection is $\beta x/(\delta + \nu + c)$.

By convention, R_0 is the number of secondary infections caused by a single infected host when introduced into a population of uninfected hosts. When there are no infected hosts, $y = 0$, and the host population size can be obtained from $\theta - \delta x = 0$, or $x = \theta/\delta = N$. Using $x = N$, the number of secondary infections in an uninfected populations is R_0 in Equation (16).

If R_0 is larger than one, then the parasite will spread in an initially uninfected population.

Damped oscillations will lead to the stable equilibrium

$$x^* = (\delta + \nu + c)/\beta$$
$$y^* = \frac{[\beta\theta - \delta(\delta + \nu + c)]}{\beta(\delta + \nu + c)} . \quad (18)$$

A simple extension of Equation (17) with two parasite strains can be used to study natural selection of parasite traits. This analysis shows the conditions that favor the parasite strain with the highest R_0. The extended dynamical system is (Nowak and May 1994)

$$dx/dt = \theta - \delta x - x(\beta_1 y_1 + \beta_2 y_2)$$
$$dy_1/dt = y_1(\beta_1 x - \delta - \nu_1 - c_1)$$
$$dy_2/dt = y_2(\beta_2 x - \delta - \nu_2 - c_2) ,$$

where y_1 and y_2 are the number of hosts infected by parasite strain one and strain two, respectively. Each strain has its own set of parameters for transmission, virulence and clearance, β, ν and c. I assume here that each host has only one of the two parasite strains.

The evolution of parasite transmission, virulence and clearance can be studied in equilibrium and nonequilibrium systems. At equilibrium, the host-parasite system tends to settle to a steady-state number of infected and uninfected hosts, as in Equation (18). If strain two is absent, and R_0 for strain one is greater than one, then the system settles to an equilibrium with $x^* = (\delta + \nu_1 + c_1)/\beta_1$ uninfected hosts. The condition for parasite strain two to invade this population and increase in frequency is $dy_2/dt > 0$, which implies $(\beta_2 x - \delta - \nu_2 - c_2) > 0$. Using the equilibrium abundance of uninfected hosts, x^*, parasite strain two increases only when

$$\beta_2/(\delta + \nu_2 + c_2) > \beta_1/(\delta + \nu_1 + c_1) ,$$

which is another way of saying that a parasite strain can always invade an equilibrium system if it has a higher R_0 than the resident parasite, and resist invasion by parasite strains with lower R_0 (Levin 1983; Nowak and May 1994). Thus, in equilibrium systems, evolution favors parasites with the highest R_0 (Bremermann and Thieme 1989). Recall that R_0 is proportional to the number of secondary (progeny) infections produced by each infected host. In a stable (equilibrium) system, number of progeny is an accurate measure of fitness. Thus, the optimal parasite parameters for transmission, virulence and clearance can be found by expressing transmission and clearance in terms of virulence and maximizing $R_0 = \beta(\nu)N/[\delta + \nu + c(\nu)]$, as discussed above (see Equation (10)).

In some cases equilibrium analysis is inappropriate. For example, in bacterial epidemics that occur among hospital patients, the infection is initially rare and spreads quickly (Ewald 1994). Control measures, such as antibiotics or isolation of infected individuals are typically used and greatly reduce or eliminate the epidemic. To understand the severity of disease in such cases, it is necessary to consider how virulence evolves in nonequilibrium systems.

When parasites are absent, and new infections are introduced and spread rapidly, the parasite strain with the fastest rate of increase will dominate (Lenski and May 1994; Bull 1994; Levin et al. In press; Lipsitch and Nowak 1995). The rate of increase is birth rate minus death rate which, from Equation (17), is

$$\beta(\nu_{ia})N - [\delta + \nu_i + c(\nu_{ia})] , \quad (19)$$

where ν_{ia} is the virulence of genotype a in the ith host, ν_i is the average virulence of parasites in the ith host, and transmission and clearance are expressed as functions of virulence. Taking the derivative of this expression, evaluated at $\nu_{ia} = \nu_{ib} = \nu^*$, yields an approximate solution for the level of virulence that maximizes the rate of parasitic spread

$$(d\beta(\nu)/d\nu)N - r - dc(\nu)/d\nu = 0 ,$$

where the derivatives are evaluated at ν^*. This condition is approximate because relatedness is equal to $d\nu_i/d\nu_{ia}$ only when the system is near equilibrium. But this condition does give the proper qualitative effect on virulence caused by relatedness and within-host competition. (Processes of genetic mixing are discussed below under "Patterns of transmission.")

If there is a tradeoff only between clearance and virulence, $c(\nu) = \gamma/\nu^\tau$, with constant transmission rate $\beta(\nu) = b$, then $\nu^* = (\tau\gamma/r)^{1/(1+\tau)}$. The same result is obtained at equilibrium, Equation (13). Thus the clearance-virulence tradeoff is not affected by the dynamics of epidemics.

If we assume a tradeoff between transmis-

sion and virulence, $\beta(v) = bv^s$, as in Equation (11), and no tradeoff between clearance and virulence, $c(v) = \gamma$, then the fastest rate of parasite spread is achieved for a virulence of

$$v^* = (Nbs/r)^{1/(1-s)}. \quad (20)$$

This result is interesting because it shows that, at the start of an epidemic, virulence is strongly influenced by the opportunities for transmission, given by the number of susceptible hosts and the transmission rate, Nb. By contrast, the predicted virulence at equilibrium is independent of opportunities for transmission, but depends on the rates of host death and parasite clearance, $\delta + \gamma$, as shown in Equation (12) (van Baalen and Sabelis 1995). In spreading epidemics, the form of selection on virulence is controlled mainly by parasite "birth" rates—the transmission and infection of new hosts (May and Anderson 1990; Lenski and May 1994; Levin and Bull 1994; Levin et al. In press; Lipsitch and Nowak 1995). At equilibrium the form of selection on virulence is controlled mainly by parasite "death" rates—death of the host or clearance of the infection. In all cases lower relatedness among parasites within hosts, r, causes greater within-host competition and higher virulence.

It is easy to see why higher densities of susceptible hosts and higher transmission rates would favor higher virulence in a spreading epidemic. Consider, for example, an intestinal bacterium such as *Escherichia coli*. This bacterium normally has little effect on the health of its host, but some strains cause severe diarrhea and can kill the host. The diarrhea contains high concentrations of the bacteria, apparently enhancing transmission to new hosts. The opportunities for transmission appear to be particularly high in hospitals, and Ewald (1994) has argued that severely virulent epidemics of *E. coli* occur mostly in health care institutions where there is a high density of hosts and greater opportunity for transmission. This is an intriguing idea that I will analyse more carefully in a later section.

It is more difficult to see why the density of hosts and rate of horizontal transmission has no effect on virulence when the disease has stabilized at an equilibrium number of infected hosts. At equilibrium there is, by definition, a balance between the infection of new hosts by horizontal transmission and the loss of infection through host death or clearance. Consider what would happen to an equilibrium system if one were to increase the density of hosts or the efficiency of parasite transmission from infected hosts. More hosts would become infected until the number of available, uninfected hosts dropped, and balance is again obtained between the infection of susceptible hosts and the loss of infection through host death or clearance. At equilibrium, because the parasites' birth rate (new infections) must equal the parasite death rate (host death or clearance), changes in host density or transmission efficiency will be balanced by changes in the frequency of infected versus uninfected hosts (Lenski and May 1994; Bull 1994; Lipsitch and Nowak 1995; van Baalen and Sabelis 1995).

The balance occurs when the rate of new infections is matched by host death or clearance. In this case the parasite death rate is constant, and the density of available hosts is adjusted by changes in the proportion of hosts that are infected. Thus the equilibrium virulence depends on the parasite death rate but not on the density of hosts and the rate (efficiency) of horizontal transmission, Equation (12). I will return to this problem of virulence in equilibrium systems in a later section when I discuss Ewald's (1994) proposal that, by decreasing the efficiency of parasite transmission, one favors an evolutionary reduction in the virulence of parasites.

WITHIN-HOST DYNAMICS AND GROUP SELECTION

The previous section emphasized how the dynamics of transmission affect the evolution of virulence. In this section I briefly discuss the dynamics of competition between different parasite genotypes within a host (e.g., Levin and Svanborg Edén 1990; Levin and Bull 1994). Levin and Bull have suggested that several diseases, such as bacterial meningitis and poliomyletis, are caused by virulent mutations outcompeting other parasite genotypes within the host. I discuss the biology in a later section. My purpose here is to complete the conceptual framework for models of virulence.

In the population of parasites within a host,

a mutant parasite with a faster growth rate will usually increase in frequency. The mutant will spread even when it causes extreme virulence and rapid host death. If death occurs quickly, the mutant and its neighbors are doomed because they will not be transmitted to other hosts. The mutant has high fitness within the host, but its long-term fitness is zero. Although within-host evolution favors increased growth rate of parasites, net change in the population of parasites depends on fitness tradeoffs described in the equilibrium models.

The direction of evolutionary change in the parasite population is not affected by these highly virulent mutants. But the frequency of a particular disease could depend on the dynamics of within-host evolution rather than the average level of virulence in the population of parasites. Thus we must distinguish between evolutionary tendencies that shape the average of traits and the distribution of traits maintained by a balance between mutation and selection within hosts versus selection among hosts.

Mutation-selection balance for parasites depends on parasite population size within hosts and the number of generations within hosts relative to transmission rate. If transmission is relatively frequent compared with generation time within hosts, then selection will purge highly virulent mutations that do not contribute to long-term fitness. Slower transmission, compared with the number of generations within hosts, will maintain a greater number of virulent mutants by reducing the efficacy of between-host selection and increasing the opportunity for mutants to arise and spread within hosts.

Patterns of Transmission and Reproductive Value

Many complex aspects of epidemiology and transmission influence the evolution of parasite life history. In this section I show that several important topics can be understood in terms of *reproductive value*. Fisher (1958) defined the reproductive value of individuals of different age as their expected genetic contribution to future generations. More generally, reproductive value is the relative weighting of different fitness components or classes of individuals according to their long-term contribution to the gene pool. Life history theory uses reproductive value to translate ecological and demographic aspects of populations into fitness effects and evolutionary consequences.

Supply of Available Hosts

In the previous models the total number of new hosts born into the population occurs at a rate independent of disease. This may be true in some modern human populations. However, diseases such as measles and smallpox may have had a signficant demographic impact before the widespread vaccination of the past few decades, and HIV has the potential to influence population size in the future. The supply of new hosts may be regulated by parasites in many natural populations, but regulation is difficult to demonstrate conclusively. Regulation is implicated in rabies-fox interactions and a few other well-studied cases (see Anderson 1991 for a summary of these topics.)

Lower virulence is favored when parasites reduce the supply of new hosts because there are fewer opportunities for transmission (Lenski and May 1994). This conclusion can be understood by analysing the reproductive value of the parasites' fitness components. Fecundity is the number of new infections produced by a parasite per unit time. Survival is the probability that an infection maintains itself within a host for a given time period. Higher virulence means lower survival. A tradeoff is assumed between transmission (fecundity) and virulence (survival).

The transmission (fecundity) component of fitness depends on the host population. Fewer new hosts lead to fewer parasite progeny per unit of investment in transmission. The parasites' survival component of fitness is the same, whether the supply of new hosts is regulated by parasites or by extrinsic factors, because lower virulence increases parasite survival independently of host density. Thus parasite regulation of the host supply, causing relatively lower valuation of fecundity, favors relatively lower transmission and virulence.

The same life history analysis applies to the epidemic models of the previous section. In epidemics, with a large supply of available hosts, a parasite can trade reduced survival

(increased virulence) for the opportunity to produce many progeny. Likewise, a growing host population favors high parasite fecundity and virulence, whereas a shrinking host population puts a premium on parasite survival and reduced virulence (Lipsitch and Nowak 1995). The general observation that population demography influences the relative valuation of survival and reproduction was discussed by Fisher (1958) in the original formulation of reproductive value.

NONRANDOM MIXING

The previous models assumed random mixing of hosts, so that the supply of available hosts is the same to all parasites. This may be approximately true for air-borne transmission of highly infectious parasites. By contrast, venereal transmission and many types of vector-borne transmission are likely to cause a high correlation in infection status among hosts that the parasite can reach.

Nonrandom transmission can influence parasite life history in a variety of ways. For example, the number of contacts among the same host individuals changes the tradeoff between transmission and virulence. Lipsitch et al. (1995a) have argued for a law of diminishing return that reduces virulence as the number of repeat contacts increases between pairs of hosts. With a high rate of repeat contact, low virulence and low transmission per contact approach the same net transmission rate as high transmission per contact. Thus increasing virulence has diminishing transmission benefits. In terms of the models above, with transmission rate $\beta(v)$ proportional to v^s in Equation (11), increasing contact causes a decline in s and a reduction in equilibrium virulence in Equation (12).

SECONDARY INFECTION

The supply of uninfected, susceptible hosts declines as a disease spreads. This can influence epidemiology and the evolution of virulence in different ways, depending on the probability that a parasite can invade an already infected host (secondary infection). In this section I consider the role of secondary infection under the assumption that there is a tradeoff between virulence and transmission.

The dynamical model, Equation (17), that leads to the particular R_0 expression used earlier, Equation (16), assumes that parasites can colonize and succeed only in uninfected hosts. Genetic variability in hosts arises only by mutation or simultaneous infection. Lack of secondary infection leads to an interesting interaction between epidemiology and the evolution of virulence. Closer crowding of hosts or other factors that increase transmission efficiency increase the frequency of infected individuals and reduce the supply of available hosts. At equilibrium, however, this has no effect on the evolution of virulence because the higher transmission efficiency is exactly balanced by the lower supply of hosts (see above). The net rate of transmission is unchanged and equals the rate at which infections are lost from hosts by death or clearance.

Models that study secondary infection are more complicated. They must keep track of different parasite genotypes, because it is only secondary infection by a different genotype that has evolutionary consequences. Assumptions must also be made about within-host dynamics. One possibility is that a secondary infection either fails completely or outcompetes the resident and takes over the host. Competitive exclusion within hosts has been called "superinfection" (Nowak and May 1994; May and Nowak 1994). These authors define secondary infection with maintenance of multiple types as "coinfection."

In models of competitive exclusion (superinfection), the more competitive genotypes are assumed to cause greater virulence and, consequently, shorter residence times within hosts (Nowak and May 1994). Thus intermediate levels of virulence are favored because of the tradeoff between higher competitive ability (virulence) and lower net transmission per infection. An increased level of multiply infected hosts favors more competitive and more virulent parasites, as found in a variety of other models (see above). Thus, with secondary infection, increased crowding or transmission efficiency may cause increased within-host competition among genotypes and the evolution of higher virulence.

The competitive exclusion models can maintain complex patterns of parasite polymorphism with a multimodal distribution of parasite phenotypes. It seems likely that these

complex polymorphisms depend on the assumption of competitive exclusion within hosts by the superior genotype. Because a tiny competitive advantage leads to complete dominance in a host, small phenotypic differences cannot be maintained in the population. Large phenotypic differences are maintained by aspects of nonlinear interactions that are not fully understood.

A model, such as Equation (3), in which competitive success is a linear function of phenotype, is unlikely to maintain multimodal polymorphisms. Thus different assumptions lead to different predictions about polymorphism. The next question concerns the realism of the assumptions for the competitive exclusion and linear success models. On the one hand, competitive exclusion is unlikely between strains that have only minute phenotypic differences. On the other hand, small differences in growth rate can lead to large differences in population sizes among parasite genotypes if there are many parasite generations within each host. Thus the realism of the alternative models may depend on within-host dynamics.

The epidemiological consequences of secondary infection are not fully understood. It must be that, for each genotype at equilibrium, the rate at which infections are lost by competition, clearance or host death equals the rate at which new infections are established by transmission.

HORIZONTAL VERSUS VERTICAL TRANSMISSION

Vertical transmission limits the success of a parasite to the survival and fecundity of its host. Therefore vertical transmission tends to reduce virulence when compared with horizontal transmission, which allows new infections to offset parasite losses from host death. But the simple generalization that virulence will increase with the ratio of horizontal to vertical transmission can be misleading.

Consider the simple case with uniparental, vertical transmission and no horizontal transmission. If the parasite reduces host fitness, then it will be lost from the population (Fine 1975): Any reduction in host fitness will cause the frequency of infected hosts to decline relative to that of uninfected hosts. Thus vertically transmitted parasites must be harmless or beneficial to their hosts. This conclusion is formally correct but may be misleading.

Vertically transmitted, obligate symbionts can evolve to cause significant harm to the host. The relative harm to the host increases as the coefficient of relatedness declines among symbionts within hosts (Equation (4), Figure 1). The average fitness of symbionts within a host is matched to the host's fitness, but selection maximizes average group fitness only when group members are closely related or do not compete for limited resources.

Any symbiont that has a net positive effect on host fitness can spread to fixation under purely vertical transmission. However, the symbiont may be beneficial with respect to one trait, providing new biochemical pathways for host metabolism, and harmful in other traits, such as destruction of host tissue. Only symbionts with a net positive effect can be maintained. But a character such as tissue destruction is subject to selection for virulence according to the simple models presented earlier. It is misleading to measure virulence only by net effects. Such a holistic view obscures interesting evolutionary problems that arise when host and symbiont fitness conflict over certain traits. Vertical transmission alone cannot explain the wide variation in fitness effects that symbionts are predicted to have on their hosts as a function of relatedness within hosts.

The idea that vertically transmitted parasites cannot harm their hosts is usually thought of in a context where some hosts are infected and others are not. The infected hosts and their parasites necessarily decline in frequency and disappear if the parasites are harmful. But how likely is it that we would observe a mixture of infected and uninfected hosts under purely vertical transmission? Advantageous parasites spread to fixation, disadvantageous parasites disappear. Neutral parasites drift in frequency and eventually become extinct. Only some form of balancing selection can maintain a stable mixture of infected and uninfected hosts.

One probable explanation for the fact that some hosts are infected and others are not is that purely vertically transmitted parasites are rare. There may be mixing of symbionts from the two parents or occasional horizontal transmission. With mixing of lineages or horizontal

transmission the parasites can be maintained in spite of net deleterious effects on their hosts.

Lipsitch et al. (1995b) have shown that it is difficult to measure the relative importance of vertical and horizontal transmission. I find their results easiest to understand by restating them in terms of life history theory. Horizontal transmission is a fitness component that can be equated with fecundity. Parasite survival in a lineage (vertical transmission) is a second fitness component that can be equated with longevity.

Lipsitch et al. (1995b) studied an explicit model of mixed vertical and horizontal transmission. A rough idea of their main results can be understood by a simple reinterpretation of the dynamical model in Equation (17), with the number of new, horizontally transmitted infections induced during the lifespan of each infection

$$R = \frac{\beta(\nu)NX}{\delta + \nu + c(\nu)},$$

where X is the frequency of uninfected hosts. The denominator is the rate of loss of an infection from a vertical lineage of hosts: δ is the extinction rate of the host and its descendants (host lineage), ν is death of the host lineage caused by parasite virulence, and $c(\nu)$ is clearance of the infection from the host lineage during a host's lifetime or by failed vertical transmission to the offspring. The reciprocal of the denominator is the longevity of an infection. The numerator is the number of horizontally transmitted infections caused by an infected host — the fecundity of an infection.

At equilibrium, the "death" of each infection must be balanced by a single "birth," so $R = 1$. Put another way, at equilibrium the rate of loss of infections from vertical lineages must be equal to the rate at which new infections begin by horizontal transmission. When the survival of parasites and the efficiency of vertical transmission is high, nearly all infections of hosts will be by vertical rather than horizontal transmission. An increase in the efficiency of horizontal transmission, β, increases the frequency of infected hosts, but those additional infected hosts will tend to transmit vertically rather than horizontally. Thus a population with a high frequency of infected, vertically transmitting hosts may actually imply efficient horizontal transmission.

The predicted virulence for a tradeoff between horizontal transmission and virulence, $\beta(\nu) = b\nu^s$, with no tradeoff between clearance and virulence, $c(\nu) = \gamma$, was given earlier in Equation (12) as

$$\nu^* = \frac{s(\delta + \gamma)}{r - s} \qquad r > s,$$

where r is the coefficient of relatedness among parasites within a host. High survival within host lineages and high vertical transmission efficiency (low $\delta + \gamma$) leads to low virulence, consistent with the idea that vertical transmission favors relatively benign parasites. But Lipsitch et al. (In press) showed that one cannot translate this conclusion into the simple prediction that the observed levels of horizontal and vertical transmission correlate with expected levels of parasite virulence (*contra* Ewald and Schubert 1989).

Consider two populations, one with a high and the other with a low observed frequency of infected, vertically transmitting hosts. The relatively high frequency of vertically transmitting hosts may be caused either by high efficiency of horizontal transmission (high b in $\beta(\nu) = b\nu^s$), or by a relatively high efficiency of vertical transmission (low δ or γ). Changes in horizontal transmission efficiency have limited effects on the predicted virulence, whereas changes in vertical transmission efficiency have a strong influence on virulence. Thus one cannot predict the expected level of virulence based on the observed frequency of vertically transmitting hosts. Essentially, the reproductive valuation of different transmission pathways is influenced by demography and epidemiology. Thus ecological aspects of transmission must be translated into reproductive valuations before drawing conclusions about parasite life history.

Once again the current models depend on the assumption of no secondary infection. It must be true that, with secondary infection, the equilibrium rate at which a genotype is lost from vertical lineages equals the rate at which that genotype infects a host by horizontal transmission. But the consequences of secondary infection for vertical and horizontal transmission are not understood at present (see Lipsitch et al. In press, for preliminary work).

In conclusion, the distinction between hori-

zontal and vertical transmission is important, but simple generaliztions can mislead. The key processes for parasite life history are relatedness, competition within host lineages, and the reproductive valuations of survival and fecundity in the context of epidemiology.

REPRODUCTIVE VALUE OF HOSTS AND HABITATS

Many other factors influence the evolution of parasite traits. Suppose, for example, that the course of infection varies in different kinds of host. What will happen if, for the virulence-transmission tradeoff, a parasite is well balanced (near equilibrium) in one host, but quickly kills hosts of a second species? Parasites infecting the second host contribute very little to future generations, so there is little selection favoring changes in the parasite traits. The strength of selection on parasites in each habitat is proportional to the reproductive value of that habitat (Holt 1996), where reproductive value is the expected contribution to future generations.

Paradoxically, extreme virulence in some hosts prevents the evolution of moderation because those hosts contribute few parasites to future generations. Selection will emphasize the fitness consequences of parasite traits within the other hosts that maintain the parasite population. Thus highly virulent disease in one type of host can be evolutionarily stable if there is a second type of host nearby that maintains a supply of the parasite. The basic tradeoff theory remains intact, but one needs to weight the selective pressure in each host type by the reproductive value of the parasites from that host (Holt 1996). Similarly, selection in different tissue types (habitats) within a host must be weighted by the reproductive value of parasites in those tissues, as in the meningitis example discussed earlier.

SENESCENCE OF INFECTIONS

Another type of classification by reproductive value is the time since infection, that is, the age of the parasite population in the host. With classification by time, the well-developed theory of aging can be applied (Rose 1991). The strength of selection is inevitably greatest for traits that influence new rather than old infections because all infections pass through a new stage, but many fail to reach "old age" (May and Anderson 1990; Levin and Bull 1994; Levin et al. In press). Thus parasite traits are often favored if they cause increased success early in the infection but have costs, such as high virulence, later in the cycle. Also, the force of selection is weak on traits that affect only the later stages of an infection cycle. Thus maladaptive virulence for old infections can be maintained in high frequency by mutation-selection balance.

SUMMARY OF THE THEORY

I have emphasized five factors in the evolution of virulence.

(1) *Tradeoff between transmission and virulence.* A parasite character may affect both transmission rate and virulence. Faster transmission is advantageous because it is equivalent to a greater reproductive rate. Virulence is disadvantageous because it reduces resources available for future reproduction and decreases the expected life span. As in all models of life history evolution, selection favors a balance between fecundity and longevity (Roff 1992; Stearns 1992).

(2) *Tradeoff between clearance and virulence.* Host defenses attempt to clear infections from the body or localize infections to prevent their spread. Parasite characters that avoid clearance may cause damage to the host. For example, a simple parasite character such as increased reproductive rate within the host may reduce the rate of clearance but also increase the damage to the host.

(3) *Genetic variability and kin selection.* Parasite genotypes that use up the host resources quickly may outcompete their neighbors within a host. Rapid exploitation may, however, increase virulence and reduce the resources available from the host. Selection favors a balance between success within the host, favoring high competitive ability and high virulence, and prudent exploitation of the host, favoring low virulence. I analysed this balance by applying the theory of kin selection. The optimal balance is expressed in terms of the coefficient of relatedness among competing parasites. Low relatedness favors intense competition within the host and high virulence; high relatedness favors cooperation and prudent exploitation.

The coefficient of relatedness is affected by

three processes. First, mutation of parasites within hosts decreases relatedness. Second, the number of parasite individuals sampled during each transmission event determines the size of the founding population in new hosts. Smaller samples cause a narrow population bottleneck and higher relatedness. Finally, mixing of parasite lineages decreases relatedness. Lineages may be mixed by multiple infection of hosts or by mixing within vectors that pick up parasites from different sites.

The effect of relatedness within hosts depends on the mechanisms of transmission and clearance. Suppose, for example, that transmission rate increases with the number of lesions, and all strains gain equally from each lesion. There is no conflict among genotypes because transmission success per lesion is shared equally by all genotypes. Thus the coefficient of relatedness has no influence on the evolution of parasite life history. By contrast, if the transmission rate of a mosquito-borne pathogen depends on the relative concentration of pathogens in the blood, then the relative reproductive rate of pathogens translates directly into transmission rate. The pathogens are in direct competition, and the coefficient of relatedness has a strong effect on parasite life history.

The tradeoff between clearance and virulence is also affected by the particular mechanism of clearance. If all genotypes are cleared at the same rate, then relatedness has no influence on life history. By contrast, if a parasite trait affects both virulence and a genotype's relative rate of clearance, then relatedness affects parasite evolution. A simple example is reproductive rate. Fast reproduction may allow a genotype to last longer in the race against the host's clearance system while increasing the damage caused to the host.

There is one additional effect of relatedness on parasite life history. When relatedness within a host is high, then parasites are often competing for resources against genetically identical neighbors. Selection may, as a consequence, favor traits that carry a portion of the parasites to new locations in order to compete against nonrelatives (Hamilton and May 1977). The fraction of dispersing parasites favored by selection can be very high, even though the opportunity for successful transmission is low. Dispersal is high in this case because the potential fitness gains are low for staying home to compete against relatives.

I summarized a model in which a single parasite trait influences competitiveness within hosts, virulence, and dispersal rate. The model is obviously a simplification because many parasite traits influence these three components of fitness. Nonetheless, the results are interesting and not easily predicted from intuition. To repeat just one example from the models, consider how the success rate of dispersing parasites (the parameter c in Figure 6) influences life history traits. The fitness benefits of dispersal decline as the probability of successful dispersal decreases. However, low success in transmission may decrease the number of different parasites that colonize each host, which in turn increases the relatedness among parasites within hosts. High relatedness means intense competition among relatives, which favors increased dispersal in spite of the low chances for success.

This complicated web of interactions requires attention to the assumptions and consequences for particular host-parasite systems. Even very simple life history tradeoffs can lead to surprising results.

(4) *Nonequilibrium dynamics*. The previous conclusions follow from the equilibria in a variety of models. Nonequilibrium dynamics always pose a challenge to any simple framework. The main message from the past twenty years is that simple, nonlinear interactions can lead to very complicated and unpredictable dynamics (May 1986). If it turns out that every pattern of virulence is indeed complex and unpredictable because of nonlinear dynamics, then there is no possibility of explaining why parasites have particular life history traits. We do not know if things will turn out so badly. Thus the best approach for now is to keep the theory as simple as possible so that systematic differences between theory and observation can be recognized and understood. To me there seems little question that the processes of kin selection and tradeoffs in fitness components do occur frequently. One problem is how much of the observed variation can be explained by these simple processes. A second problem is whether the current con-

ceptual framework expresses these processes in a correct way.

Returning from these philosophical issues to the models themselves, there were two simple conclusions about nonequilibrium dynamics that fit easily into the framework of adaptive tradeoffs. The first concerns how the dynamics of epidemics affect the direction of evolutionary change. Rapidly spreading diseases emphasize the transmission component of fitness. When there is a tradeoff between transmission and virulence, epidemics favor parasite traits with greater rates of transmission and higher virulence relative to the traits favored by endemic diseases.

The second conclusion about nonequilibrium dynamics concerns within-host evolution. New parasite mutations spread within a host if the mutant has a competitive advantage relative to its neighbors. The consequences of high virulence are irrelevant because, in the host, success depends only on the relative reproductive rate with respect to the local population. However, mutants that succeed in the host will not spread if they cause host death before they can be transmitted. Thus the average trait values of parasites are determined by the adaptive tradeoff theories, but rare mutants with high virulence can be maintained by mutation-selection balance.

(5) *Patterns of transmission and reproductive value.* I discussed these topics in the previous section. Briefly, the main point is that parasites are transmitted in different ways. The adaptive allocation of parasite resources to different transmission pathways depends on the reproductive value weighting of each pathway. Reproductive value is the contribution to future generations.

For example, survival and reproduction are two pathways by which a parasite can contribute genes to a later time period. It is convenient to think of parasite survival as maintenance of infection within a host and reproduction as horizontal transmission and infection of new hosts. A large supply of new hosts increases the reproductive value of horizontal transmission, favoring parasite reproduction at the expense of higher virulence and lower survival. However, greater transmission may quickly use up the supply of new hosts, reducing the value of horizontal transmission relative to survival. Thus the parasites' reproductive value of transmission (reproduction) and virulence (survival) depend on the epidemiology of the infection, and the epidemiology depends in turn on the evolution of parasite life history.

Similar problems arise when analysing the evolution of parasite life history in different hosts or when comparing the valuation of vertical transmission versus horizontal transmission. In each case the only way to analyse life history is to carefully unravel the effects of epidemiology and evolution on the reproductive value of each component of parasite fitness.

Four Examples

In the following sections I present four case studies. These examples illustrate how simple concepts can be applied to real problems. There are many fine studies on virulence to choose from. I picked these examples because each discusses interesting data and interprets those data in light of evolutionary theories of virulence. In each case my interpretations differ slightly from the those presented by the authors. The differences are relatively minor because the authors and I share the same basic evolutionary framework. However, the differences of interpretation highlight the locus of debate in this active field, and show how carefully one must apply even the simplest theory.

Multiple Infection and Nematode Virulence

Fig trees are pollinated by tiny wasps (Janzen 1979; Wiebes 1979). These wasps often carry parasitic nematodes. Herre (1993) found that the virulence of the nematodes increased when there was more contact among wasps. He noted that increased virulence occurs when there is greater opportunity for horizontal transmission of the nematodes. This supports a commonly discussed theory, that higher virulence is favored when the frequency of horizontal transmission increases relative to vertical transmission (e.g., Ewald 1987; Yamamura 1993). In this section I summarize the natural history of this system. I then show that, by itself, opportunity for horizontal transmission probably has little influ-

ence on the evolution of nematode virulence. Variable relatedness among the nematodes that compete for hosts is a more likely explanation for the observed patterns of virulence.

The inflorescence of figs contains hundreds of tiny flowers within a sealed cavity. Female pollinator wasps arrive at a receptive fig and push their way in through a tiny opening. Once inside, the wasps lay eggs in the ovaries of some of the flowers, they pollinate other flowers with pollen carried from the fig in which they were born, and then they die. After several weeks the male offspring emerge and mate with female offspring inside the sealed fig. The females then obtain pollen from the fig, fly off to find a new fig, and continue the cycle.

Fig wasps often carry parasitic nematodes. These nematodes enter the fig with the female wasps. While inside the fig the nematodes begin to consume the body of their host wasp. Eventually about six or seven adult nematodes emerge from the body of the dead wasp. The adult nematodes mate and lay their eggs within the fig. The nematode progeny hatch and crawl onto the emerging offspring of the wasps. These nematodes are thus carried to the next fig and continue the cycle.

Herre measured the virulence of a nematode as the relative number of progeny of infected and uninfected wasps. These data can be collected by comparing the number of progeny wasps emerging from infected and uninfected figs with only one foundress wasp. A "foundress" is a female wasp that lays eggs within a fig.

Herre predicted that fig species with a higher number of foundress wasps per fig would have more virulent nematodes. He presented two explanations. In the main text of the paper, he reasoned that if there is only one foundress in each fig, then the nematodes are transmitted vertically and their success depends on the number of progeny produced by the wasps. With vertical transmission, the reproductive interests of the wasps and the nematodes coincide. As the number of foundresses in a fig increases, the nematodes have greater opportunities for horizontal transmission. Thus the costs of increased virulence, with fewer progeny produced by the host wasp, can be balanced by attacking the host more aggressively and producing offspring that succeed through horizontal transmission.

This first explanation is the standard model of horizontal transmission favoring high virulence and vertical transmission favoring low virulence (Axelrod and Hamilton 1981; Ewald 1987; Yamamura 1993). Herre added a footnote (note 21) to his paper in which he argues that genetic relatedness among competing nematodes is the actual process influencing the evolution of virulence. More foundresses cause greater mixing of nematode lineages within figs, reducing relatedness and increasing the predicted virulence.

These two theories, horizontal versus vertical transmission and genetic relatedness among competing parasites, are often mixed together. The nematode-fig system provides a good opportunity to analyse the relationship between these theories.

Herre tested his prediction that nematode virulence would increase with greater numbers of foundresses per fig by studying 11 different species. Each fig wasp species is specialized to pollinate only a single fig species, and each nematode is specialized to attack only a single species of fig wasp. The wasp species are all closely related, and the nematode species are probably closely related as well. Thus differences among these closely related species arise from recent evolutionary changes that would most likely be explained by changes in the selective pressures among species. The data from these 11 species support the hypothesis that nematode virulence increases with greater numbers of foundresses per fig (Figure 7).

Herre's first model and his results support the widely held belief that the relative rate of vertical versus horizontal transmission is a key factor determining the evolution of parasite virulence. However, I will apply the theory developed in the previous sections to show that the evolutionary causes of virulence are more likely to be the population structure (relatedness) of the parasites and the modes of competition among parasites (as mentioned in Herre's footnote).

Horizontal versus vertical transmission is correlated with parasite relatedness and modes of competition, but in this case it may be misleading or incorrect to emphasize pat-

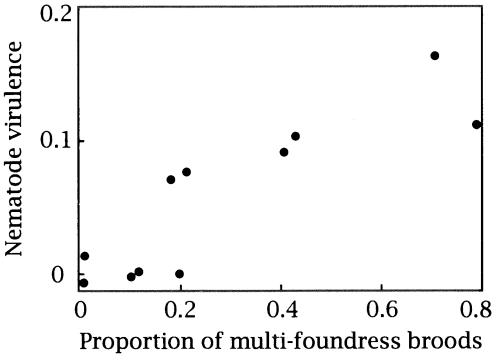

FIGURE 7. THE VIRULENCE OF NEMATODES INFECTING FIG WASPS AS A FUNCTION OF THE PROPORTION OF FIGS WITH MORE THAN ONE FOUNDRESS

Virulence is measured as $1 - f_i/f_u$, where f_i and f_u are the fecundity of infected and uninfected wasps, respectively. Fecundity is measured in figs with only one foundress. Data from Herre (1993).

terns of transmission as evolutionary causes of virulence. Suppose, for example, that many foundresses colonized each fig and that the infection rate is sufficiently low that most figs have either zero or one infected foundress. There is great opportunity for horizontal transmission. But what advantage would a nematode gain by being more virulent? There are three factors that must be considered to relate the number of foundresses and the opportunity for horizontal transmission to the expected level of nematode virulence. (i) For a given number of foundresses, how many progeny wasps are produced and available to be infected? (ii) What is the ratio of the number of progeny wasps to nematode eggs? (iii) How does nematode fecundity affect virulence, which in this case is measured by the production of progeny wasps? For this example, in which there is at most one infected foundress, there are three interesting cases that illustrate how natural history may influence virulence.

First, if there are always more nematode eggs than progeny wasps, no matter how many foundresses, then it is disadvantageous to the nematode to increase egg production and decrease its host's productivity in response to foundress number. Fewer progeny wasps caused by a more virulent nematode translates into fewer susceptible vectors. Increased virulence is not associated with a transmission advantage.

Second, if the number of progeny wasps is independent of foundress number, then the nematode gains no advantage from higher egg production and greater virulence when there are multiple foundresses. Wasp progeny number could be limited because there is a limited supply of oviposition sites within a fig.

The third case is the converse of the first two. If the number of progeny wasps increases with foundress number and, with many foundresses, the number of progeny wasps exceeds the number of nematode eggs, then nematode egg production and virulence would be expected to rise with foundress number.

The point is that horizontal versus vertical transmission is correlated with foundress number but, by itself, has no direct influence on the evolution of parasite virulence. A tradeoff between transmission success and virulence is also required. The natural history of this system may match the first case, in which no tradeoff occurs.

Now consider a second example in which all foundresses are infected. In this case virulence will be favored to rise with increasing numbers of foundresses. The cause is competition among the nematodes for access to progeny wasps and reduced relatedness among nematodes within a fig (Equation (4)). Reduced relatedness occurs when the nematodes carried by different foundresses are mixed within a fig.

Once again, the number of foundresses and opportunities for horizontal transmission are correlated with the factors that promote virulence, but horizontal transmission by itself is not the cause of increased virulence. This distinction between correlation and cause can be illustrated by an example in which there are several foundresses per fig, but the relatedness among nematodes varies. In this case there is a constant ratio of horizontal to vertical transmission because all figs have the same number of foundresses. Low virulence is favored when the nematodes are closely related. High virulence is favored when the nematodes are distantly related and compete for access to progeny wasps. Horizontal versus vertical transmission does not, by itself, control the level of virulence favored by selection.

In summary, patterns of horizontal versus vertical transmission are often correlated with relatedness and tradeoffs. But it is easy to make mistakes if one does not carefully translate the ecology and demography of a particular example into consequences for competition, kin selection, and the components of fitness.

VIRULENCE OF HOSPITAL INFECTIONS

Many bacteria such as *Escherichia coli* are typically benign within human hosts (Davis et al. 1990). Highly virulent strains occasionally arise in hospitals and nursing homes, however, causing severe epidemics and high mortality. Ewald (1994) has summarized the history of hospital epidemics caused by *E. coli*, *Salmonella*, *Staphylococcus* and *Streptococcus*. He suggested that typically benign pathogens are often highly virulent in hospitals because of the greatly enhanced opportunities for horizontal transmission. These opportunities arise from the high density of nurses, doctors and other attendants who continually touch sick patients and their effluvia, and carry transmissible pathogens to uninfected patients.

In this section I briefly summarize neonatal diarrhea caused by *E. coli* as described by Ewald (1994), and consider his theory of attendant-borne transmission as it relates to the dynamics of epidemics and the evolution of virulence.

E. coli usually has little effect on the health of its human hosts. Some strains, however, cause severe diarrhea that can kill a substantial portion of infected babies. Sick individuals often excrete very high densities of the pathogen, whereas healthy individuals pass much lower densities. Ewald summarizes several hospital epidemics that were documented in the 1940s and 1950s. By the mid-1950s, *E. coli* was recognized as a major cause of hospital outbreaks. Antibiotics and isolation of sick individuals have greatly reduced the frequency of such epidemics.

According to Ewald's theory, greater opportunity for horizontal transmission strongly favors the evolution of increased parasite virulence. The history of hospital epidemics is consistent with this theory. Attendant-borne transmission in health-care institutions and the high density of susceptible hosts provide much higher potentials for horizontal transmission than would occur outside such institutions. As predicted by Ewald's theory, virulent epidemics usually begin in these institutions.

To evaluate Ewald's theory more carefully, we must consider the models developed in the previous sections. This analysis will show that attendant-borne transmission is a plausible explanation for the high virulence observed in hospital epidemics. However, the models suggest aspects of the biology that must be studied more carefully to understand virulence, and point to factors besides attendant-borne transmission that should be considered.

Three factors are particularly important: (i) Dynamics: Is the disease spreading epidemically or is it maintained endemically with stable numbers of infections? (ii) Tradeoff: Is damage to the host an outcome of the parasites' mechanisms for evading host defense, leading to a tradeoff between virulence and clearance? (iii) Relatedness: Are there multiple infections in each host or numerous mutations of the parasite population within hosts, leading to reduced relatedness and strong competition among parasite strains within hosts?

EPIDEMIC VERSUS ENDEMIC INFECTIONS

Some pathogen strains cause occasional, virulent epidemics that spread rapidly and are then brought under control. Ewald has focused on these spectacular epidemics, in which many patients died within a short period. Other pathogens may persist for months or years in hospitals and health-care institutions, causing endemic diseases with strains that occur only in these unusual environments.

The theory developed in the previous sections shows an interesting contrast between epidemic and endemic diseases. When infections are spreading, selection enhances traits that increase the rate of transmission at the expense of shorter duration of infection. For example, diarrhea may produce very high concentrations of transmissible bacteria in the feces but can kill the host. If there are many accessible, uninfected hosts, the premium will be on transmission with a concomitant rise in virulence.

An endemic disease, by contrast, places a premium on the duration of infection. This

is a slightly more complicated conclusion because it requires tracking several consequences of a change in host density or transmission efficiency. As an example, imagine a *Staphylococcus* infection that occurs at a low, but constant (endemic) frequency in a hospital. Now suppose that the patients are crowded more closely and with fewer hygienic precautions. The opportunities for horizontal transmission have greatly increased.

The infection may appear, at first, as an epidemic, but eventually it settles to a new endemic frequency. The new frequency is higher because the transmission frequency has increased. This makes sense intuitively; when conditions first change, each bacterium released from an infected host has a greater chance of colonizing an uninfected host. The increase in the frequency of infection at the new, endemic steady-state can be calculated from Equation (18), using a higher value for transmission rate, β.

With greater opportunities for horizontal transmission, it would seem that parasites would be favored to increase transmission at the expense of the duration of infection. In particular, duration of infection is decreased by higher virulence, which reduces the hosts' chances of survival. Yet, endemic frequencies balance when opportunities for horizontal transmission are constant. When host densities increase, the frequency of uninfected hosts declines, and the density of potential targets for horizontal transmission is unchanged. Thus, in endemic diseases, the evolutionary forces that influence virulence are not affected by changes in transmission efficiency or host density. Instead, the premium is on duration of infection in the host. This explains why the level of virulence is independent of host density and transmission efficiency in the prediction

$$\nu^* = s(\delta + \gamma)/(r - s) \qquad (21)$$

given originally in Equation (12). Here δ is the hosts' natural death rate, γ is the rate at which infections are cleared by the hosts' immune system, and r is the coefficient of relatedness among coinfecting strains (relatedness is discussed below). The tradeoff between virulence, ν, and transmission rate, β, is $\beta = b\nu^s$, where b is the transmission efficiency for a given level of virulence and s determines the shape of the tradeoff between virulence and transmission (see Equation (11)).

This prediction for virulence shows that selection puts a premium on the duration of infection in endemic diseases. In Equation (21), we can compare virulence (rate of host death caused by disease) to the other factors that can end an infection: host death by other causes, δ, and clearance of the infection, γ. When the other factors, $\delta + \gamma$, are large, then the infection will not last very long, and high virulence has less cost because the infection was doomed to end soon. Thus high virulence is favored if patients are dying rapidly from other causes, or if infections are being cleared in an efficient manner by antibiotics and other treatments. On the other hand, when hosts are unlikely to die and infections are persistent (low $\delta + \gamma$), then virulence has a large impact on the duration of infection and relatively lower virulence is favored.

To sum up, the distinction between epidemic and endemic diseases is important. In epidemics, host density and transmission efficiency strongly influence the evolution of virulence; the duration of infection has much less importance. By contrast, endemic infections place a premium on duration of infection, and virulence is not influenced by opportunities for transmission.

CLEARANCE VERSUS VIRULENCE

Ewald focused on the tradeoff between transmission and virulence, but the parasites' tradeoff between clearance and virulence may also be important. For both epidemic and endemic situations, the predicted virulence when there is no tradeoff between virulence and transmission is

$$\nu^* = \left(\frac{\gamma\tau}{r}\right)^{1/(\tau+1)}, \qquad (22)$$

where r is relatedness within hosts, and the tradeoff between clearance, $c(\nu)$, and virulence, ν, is given by $c(\nu) = \gamma/\nu^\tau$ (see Equation (13)). Why would there be a tradeoff between virulence and clearance? Often there may be a race within a host between the rate at which the parasite reproduces and the rate at which the host's immune system clears parasites. For

a parasite to survive within the host, it must replicate quickly enough to outpace the host's immune system. Fast replication may destroy host cells, causing an increase in virulence. Higher replication and virulence lead to slower clearance. This idea is part of the original R_0 theories of virulence reviewed in the previous sections.

If virulence is influenced more strongly by the parasites' problems of clearance rather than transmission, what are the implications for hospital infections? From Equation (22), there are two factors to consider: the clearance constant, γ, and the relatedness of parasites, r.

Many special circumstances of hospital disease may influence the clearance constant. Infections are treated quickly and with a powerful array of drugs, which increases clearance and thus favors greater virulence. As in the previous case, when clearance is fast the infection will not last very long, and so high virulence has less cost in terms of the time period of infection. On the other hand, patients are usually sick and may not be able to mount an effective immune response, lowering the clearance rate and favoring more benign strains of parasites.

Ewald (1994) suggested that antibiotic treatment in hospitals would favor lower virulence because more virulent strains would be treated more aggressively. However, rapid clearance by antibiotic treatment tends to favor higher virulence, as shown in Equation (22). Thus antibiotics may favor very low parasite virulence to avoid detection and treatment or very high virulence to outrace treatment and obtain the greatest reproduction in the shortest period. This is a form of disruptive selection, in which extreme traits are favored and intermediate traits have low fitness.

A problem of classification must also be considered. The same parasite strain may cause a more severe infection in a weakened patient than in a healthy individual. When analysing the evolutionary processes that influence virulence, it is not meaningful to describe this single strain as more virulent in the sick patient. Rather, the problem is one of comparison. For two different parasite strains, which is more virulent in the same host and under the same conditions? What are the fitness consequences of differing virulence between the two strains with respect to transmission and clearance when measured in similar hosts?

In summary, within-host dynamics and clearance may in some cases be a more important process than the transmission-virulence tradeoff (Anderson and May 1982; Antia et al. 1994; Levin and Bull 1994).

KIN SELECTION

Another factor that may explain greater virulence of hospital infections is the relatedness among parasites within hosts. Lower relatedness occurs when there are multiple infections by different parasite strains or when populations of the parasite mutate within the host. Low relatedness favors stronger within-host competition among parasite strains, promoting each strain to "use up" the host quickly to prevent the other strains from doing so first. Higher virulence is favored by lower relatedness in all cases, both for endemic and epidemic infections, and for tradeoffs with either transmission or clearance.

Hospital environments are particularly likely to promote multiple infection by different parasite strains. Host density is high, transmission by attendants is efficient, and there are large, relatively stable pathogen populations that can maintain genetic diversity.

In summary, the problem of hospital virulence is an important public health issue and an ideal model system for the study of virulence. Ewald (1994) made an important contribution by calling attention to this topic. His theory of attendant-borne transmission may explain virulence in some pathogens, but there are several alternative processes that can affect the evolution of virulence.

EVOLUTIONARY CONTROL OF VIRULENCE

In Ewald's (1994) view the opportunities for horizontal transmission control the evolutionary pressures on virulence. He believes that lowering the rate of transmission for particular diseases will cause those pathogens to evolve lower virulence. For malaria, if we can reduce the frequency with which an infected individual is bitten, we have reduced the transmission rate.

The models in the previous sections show that, when diseases are spreading in an epidemic, the rate of horizontal transmission is

a crucial factor in the evolution of virulence (see Equation (20)). By contrast, if the frequency of infected individuals is approximately stable, then transmission efficiency has no effect on the evolution of virulence (Lenski and May 1994; Levin and Bull 1994; Lipsitch and Nowak 1995; van Baalen and Sabelis 1995). To reword one conclusion from the previous section: when transmission efficiency declines, the density of uninfected hosts rises, and the net opportunities for horizontal transmission are approximately unchanged. For malaria, a lower biting rate may be balanced by the increased probability that a pathogen-carrying mosquito will find an uninfected host.

Simple models suggest that evolutionary pressures on virulence cannot be changed for endemic diseases by altering transmission efficiency. In my analysis I have assumed that transmission efficiency is the parameter b in the tradeoff between transmission and virulence, $\beta(v) = bv^s$ given in Equation (11). In this model b is the component of transmission that is independent of virulence, such as the abundance of vectors. Here $\beta(v)$ is the transmission rate as a function of virulence, v, and s is a parameter that determines the shape of the relationship between virulence and transmission. The predicted virulence for endemic diseases, given in Equation (21), shows that b has no effect on virulence.

Increased transmission may, however, raise the rate of secondary infection. Multiple infection can lower the relatedness of parasites within hosts, r, favoring increased virulence. However, the interactions between secondary infection and epidemiology are potentially complex and not fully understood at present (see earlier section on "Secondary infection").

Other factors could also link transmission and virulence. Ewald has emphasized that virulence often immobilizes the host in vector-borne diseases. A bedridden human, too sick to swat mosquitoes, may be a more efficient source of transmission than someone who is walking about and mixing with uninfected hosts. Ewald suggested that if patients with virulent infections were isolated so that they would not be a source of high transmission, then pathogens would be favored to reduce their virulence and increase the length of infection. In terms of the tradeoff $\beta(v) = bv^s$, Ewald is suggesting that by reducing the parameter s, the rate at which parasites gain transmission from high virulence is also reduced. A reduction in s does indeed reduce the predicted virulence, as shown in Figure 3.

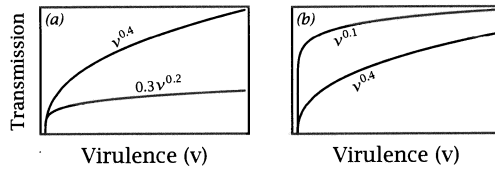

FIGURE 8. THE TRADEOFF BETWEEN VIRULENCE AND TRANSMISSION

Transmission, $\beta(v)$, is bv^s, where v is the level of virulence, b is the transmission efficiency, and s determines the shape of the tradeoff. In panel (a), the tradeoff is initially given by $b = 1$ and $s = 0.4$ in the upper curve. The lower curve is obtained when very sick individuals are sequestered in a way that reduces transmission, changing the shape of the curve ($s = 0.2$) and reducing the transmission efficiency, $b = 0.3$. In panel (b) the initial case is also given by $b = 1$ and $v = 0.4$, which in this case is the lower curve. The upper curve, with $b = 1$ and $s = 0.1$, is obtained by increasing the transmission rate from individuals with mild symptoms while keeping constant b, the overall transmission efficiency. The evolutionary consequences of these two scenarios are discussed in the text.

There are two different ways to reduce s and thereby decrease the transmission gains from very high virulence. The first, emphasized by Ewald, is to reduce the transmission from very sick hosts with highly virulent infections (Figure 8a). In this case, as s decreases the parasite gains very little with higher virulence, and thus lower virulence is favored. Here, the overall transmission efficiency, b, is also decreased, so that the frequency of transmission and infection declines. That will reduce multiple infection and increase the relatedness, r, among parasites within hosts, which also favors lower virulence (see Equation (21)).

The second way to reduce the parasites' gain in transmission for higher virulence is to *increase* the transmission from hosts with relatively benign infections (Figure 8b). In this case, higher transmission from less viru-

lent infections reduces s but does not change the overall transmission efficiency. Thus the frequency of transmission and infection increases.

Increasing transmission from relatively benign infections causes two opposing evolutionary pressures. First, lower virulence is favored because the relative transmission gains decrease for high virulence (lower s). Second, the increased frequency of infection will tend to increase the frequency of multiply infected hosts, reducing relatedness among parasites within hosts. Reduced relatedness favors higher virulence. The outcome of these opposing forces would depend on the magnitude of the parameters, the dynamics of infection, and other details of the host-parasite interaction.

My point here is not to suggest a particular strategy for public health, but to clarify the epidemiological and evolutionary processes that influence transmission and virulence. The general principles of kin selection and the tradeoffs between virulence and other components of parasite fitness will strongly influence most host-parasite systems.

Dynamics of Parasite Populations within Hosts

I have described models for parasite life histories based on tradeoffs among transmission, clearance and virulence. These three rate processes influence components of parasite fitness. No assumptions were made about which parasite characters affect these processes.

Abstraction is useful in simple models because the conclusions are not confined to particular kinds of disease. But abstract models can also be confusing because they leave out all detail about the characteristics of parasites that cause damage to the host. Levin and Bull's (1994) analysis of bacterial meningitis illustrates some of the difficulties of interpretation that may occur:

> The strains of *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae* responsible for meningitis are transmitted between hosts by droplet infection (Davis et al. 1990). Infections with these bacteria, including those of the specific strains responsible for meningitis, are usually asymptomatic. They establish and maintain their populations in the nasopharyngeal passages, and from those foci are transmitted to new hosts. In a minority of hosts, including hosts that are not compromised in their constitutive or inducible defenses, these otherwise commensal bacteria cause disease. Some of these diseases are respiratory, and the bacteria responsible for these respiratory pathologies may indeed have a selective advantage in the population of hosts because they have higher rates of infectious transmission, although this has not been formally demonstrated.
>
> In contrast, meningitis is a disease caused by these bacteria that almost certainly provides no benefit in infecting new hosts. . . . This often fatal disorder is a consequence of these bacteria infecting and proliferating in the cerebrospinal fluid, with ensuing damage to the central nervous system, primarily because of inflammatory and other host responses to the bacteria and their metabolites. The cerebrospinal fluid is clearly not a habitat that allows the infecting bacteria to be infectiously transmitted (p 77).

Host mortality (virulence) caused by meningitis is clearly detrimental to the fitness of the parasites because it kills the host quickly without any associated transmission benefits. Levin and Bull suggest that many other diseases, including polio and AIDS, provide no transmission benefits to the parasite. They interpret these cases as direct refutations of the tradeoff theories that form the basis for all previous evolutionary models of virulence. Levin and Bull's alternative "model for the evolution of virulence in pathogenic microorganisms postulates that virulence evolves within the microenvironment of individual hosts, without regard to the ultimate 'survival' (transmission) of the pathogen in the population of hosts" (Levin and Bull 1994:77). In the remainder of this section I summarize Levin and Bull's model and discuss its relationship to the adaptive, tradeoff theory of virulence.

Levin and Bull's model for virulence is based on three assumptions:

(1) The parasite develops into a large population within the host. The individual microorganisms that cause virulence are part of a genetically distinct subpopulation that arises within the host by mutation or recombination.

(2) These mutant subpopulations increase because they can reproduce more quickly than

the original population within the host, because they are better able to evade host defense, or because they colonize new tissues that the original population cannot attack. Virulence is a consequence of the mutant traits that provide increased success within the host. (3) The virulent subpopulations have reduced horizontal transmission when compared with the original population within the host.

For meningitis, Levin and Bull summarize some indirect evidence suggesting that the virulent subpopulation, crossing into the cerebrospinal fluid, arises by mutation within the host. These mutants spread because they are able to colonize a rich habitat with few competitors. Virulence occurs as a consequence of the host's response to spread in the cerebrospinal fluid and has no transmission benefit for the parasite. In fact, the mutants may be an evolutionarily doomed lineage because transmission out of the cerebrospinal fluid is rare.

Poliomyletis is a second example of this within-host model for the evolution of virulence. Only a minority of the hosts infected by the polio virus show symptoms of the disease. The site of damage in the central nervous system is not on the oral-fecal route of infection and transmission. There is not enough evidence to determine whether the virulent pathogens are a mutant subpopulation that attack tissues unavailable to the original, infecting population of pathogens within the host. Yet it seems unlikely that infection of nervous tissue, and the resulting virulence, enhance the transmission of the virus.

The third example concerns AIDS, an immunodeficiency disease caused by long-term infection with retrovirus HIV-1 or HIV-2. The progression from widespread infection but few symptoms to the later, lethal stages of immunodeficiency is not fully understood. Levin and Bull summarize three models that can explain the course of infection and disease: (i) more virulent HIVs evolve within the host (Miedema et al. 1990), (ii) HIV variation accumulates and eventually exceeds a "diversity threshold" beyond which the immune system cannot control the viral population (Nowak et al. 1991), and (iii) mutant viruses arise that cannot be recognized by the immune system (McLean 1993).

Virulence in these models results from mutation and within-host selection of the HIV population. AIDS appears to be an inevitable outcome of infection, in contrast with meningitis and poliomyletis, in which most infections are asymptomatic.

Levin and Bull argue that AIDS, the virulent symptoms of HIV, does not contribute to the transmission of the virus. Instead, AIDS develops solely as a consequence of within-host selection, with perhaps negative consequences for the fitness of the virulent subpopulation of viruses. Levin and Bull point out that there is little evidence about the stages of infection that contribute most to transmission, but they believe that the initial viremia and asymptomatic period are probably the most productive for the virus. In addition, they suggest that the severe symptoms of AIDS probably reduce social activities essential for transmission. They conclude that "based on this admittedly speculative and circumstantial argument, there are reasons to doubt the view that AIDS is an adaptation that promotes the transmission of HIV."

The question here is whether Levin and Bull's interpretations of meningitis, poliomyletis, and AIDS fit within the evolutionary framework of tradeoffs, or represent an alternative conceptual approach to the evolution of virulence. I consider the three examples in turn.

Bacterial traits that increase the probability of meningitis also greatly decrease transmission. According to the adaptive tradeoff theory of virulence, the long-term consequences of selection should strongly disfavor any trait that has the correlated effects of increased virulence and reduced transmission. This is exactly what has happened. As Levin and Bull note, the bacteria that cause meningitis infect many hosts, but rarely cause noticeable symptoms. Rare mutations may cause traits that lead to meningitis and low transmission, but these mutations do not spread among hosts. Thus the correlated traits of meningitis and low transmission are maintained in low frequency by mutation-selection balance. This is entirely consistent with the adaptive tradeoff theory of virulence. Like any theory based on natural selection, the adaptive theory emphasizes the average trait values that are expected. With meningitis, the symptoms of disease are

rare variants from the distribution of observed virulence.

The case of poliomyletis is similar. The majority of infections are asymptomatic. Viral traits that favor colonization of the central nervous system, leading to polio symptoms, are also likely to reduce transmission. Thus, to the extent that selection acts on traits that have correlated effects on virulence and transmission, the evolutionary trend will be toward reduced virulence.

Levin and Bull's model for meningitis and poliomyletis fits neatly within the adaptive framework. Their work nevertheless contributes important extensions to that theory. First, one should not mistake rare, extreme cases of virulence for the distribution of virulent effects in the pathogen population, in spite of the attention that naturally focuses on these extreme cases. Second, short-term evolution caused by mutation and selection within groups can generate rare traits that have low fitness in the population. The frequency of traits that are locally advantageous but globally deleterious depends on the dynamics of selection within and among hosts.

HIV is different because all infections are virulent, although the time of infection is long. Levin and Bull (1994) suggest that virulence (AIDS) may develop solely as a consequence of within-host selection. This hypothesis must be considered in the context of HIV life history. Here are two examples.

First, HIV traits may reduce the probability of clearance by the host immune system. For example, mutation decreases the rate of clearance by allowing the virus to alter antigenic properties. Mutation also increases evolutionary change within the host and the potential for virulence to develop. Thus, if mutation rate is subject to selective modification, there may be a tradeoff between reduced clearance and increased virulence.

Second, HIV traits that cause effects later in the infection cycle are subject to relatively weak selection (Levin et al. In press). In general, age-specific selection is weak at older ages because reproductive value is low for the class of older individuals (there are fewer of them). An epidemic further reduces the reproductive value of older relative to younger age classes. Thus virulence could be reduced by selection early in the infection because of a virulence-transmission tradeoff. Virulence may develop later as a consequence of within-host evolution at a life stage when reproductive value has declined.

For HIV and other pathogens, Levin and Bull's (1994) main point is that every case of high virulence should not be interpreted as an adaptation balanced by high transmission advantage. They emphasized within-host evolution, but that does not invalidate the adaptive tradeoff framework. Rather, their criticism highlights once again the need to analyse parasite life history in the context of each particular case. For example, meningitis may be a rare phenotype maintained by mutation-selection balance in a population of normally benign symbionts.

DISCUSSION

I have presented models for analysing parasite virulence. Very simple assumptions capture the essence of parasite life history, but the conclusions are not trivial. I mean by "not trivial" that many of the conclusions cannot be obtained without some careful thought, and that folk wisdom is as likely to be wrong as right. The favorite example, quoted by most of the recent papers on the evolution of virulence, is the myth that parasites will inevitably evolve toward a more benign relation with their hosts because damage to the host is obviously not good for the parasite. The myth is reasonable as far as it goes, but ignores the inevitable tradeoffs that form the basis for all life history analysis. When the balance is considered between fitness components of parasite life history, such as clearance, transmission and virulence, then there is no longer an inevitable evolutionary tendency toward any particular level of virulence. The predicted outcome from the simplest models depends on how the biology imposes correlations among various components of fitness.

In spite of the potential complexity from simple models, the conceptual structure is manageable. A few general processes are likely to explain a significant portion of the variation among parasites. I reviewed those processes in the summary of the models presented at the midpoint of this article. Here, I will focus on how the conceptual structure may continue to grow.

BACTERIA AND THEIR VIRUSES

Bacteria are attacked by a diversity of viruses, the bacteriophages (Birge 1994). Bacteria also carry a wide array of intracellular parasites, the plasmids (Hardy 1986). Many of the problems in parasite life history were first studied in these bacterial infections (reviewed by Levin and Lenski 1983). For example, some bacteriophages can integrate their DNA into the host genome or form free DNA circles (plasmids) that float within the cell. The viral DNA can be transmitted vertically through numerous rounds of host reproduction. During vertical transmission the viruses are typically benign or, if they carry beneficial genes such as antibiotic resistance, they can enhance the fitness of the host. These internal parasites can become highly virulent. When the switch occurs, the virus causes the host to produce many copies of the viral genome along with the viral protein coat, until the host bursts, releasing many infectious viral particles.

Plasmids also mix vertical and horizontal transmission. Vertical transmission occurs when the plasmids replicate within the cell and are transferred to daughter cells when the host divides. The plasmids can be transmitted horizontally if they carry a complex set of genes that induce a connection and transfer of genetic material between bacterial hosts.

Bacterial viruses and plasmids are parasites that can have both beneficial and harmful effects on their hosts. The life history of these parasites is subject to the same tradeoffs and evolutionary processes that I have outlined for other parasites. This connection is widely recognized, but the relation has not been fully explored between models of bacterial parasites and the generic models that I have reviewed. I will discuss only one particular set of studies on bacterial parasites—the laboratory evolution of virulence when the rates of horizontal and vertical transmission are manipulated.

Bull et al. (1991) studied the evolution of a bacterium and its bacteriophage in a controlled laboratory experiment. Several properties of the life cycle make this system a particularly good model for studying parasite life history. An infected bacterium produces bacteriophage particles (phage) continuously. Bacterial cell division continues after infection; both daughter cells typically inherit the phage. Thus these phages are transmitted both vertically and horizontally. Infected cells divide at a slower rate than uninfected cells. Infected bacteria are resistant to further infection.

Two types of phage were studied. The first was incapable of horizontal transmission and had relatively little deleterious effect on host reproduction. This "benevolent" type is a vertically transmitted parasite. The second phage type reduced host growth significantly and was capable of horizontal transmission. When the two types competed under conditions that prevented infectious transfer, the benevolent form increased in frequency. When conditions allowed horizontal transfer at a high frequency, the infectious form increased.

Bull et al. conclude from their experiments that "This study fully supports the mathematical and conceptual arguments suggesting that cooperation between a parasite and its host evolves according to the opportunities for horizontal versus vertical transmission, i.e., according to partner fidelity (Axelrod and Hamilton 1981; Anderson and May 1982; Ewald 1983, 1987; Lenski 1988; Bull and Rice 1991)" (p 880).

There is no question that opportunities for horizontal transmission can, in particular circumstances, influence the evolution of virulence. In previous sections on the formal theory and on hospital infections I reviewed models for early phases of epidemics, in which the benefits of rapid horizontal transmission can maintain high levels of virulence. However, in many other models that I reviewed, the mode of transmission did not directly affect the level of virulence, as shown in the example in which the coefficient of relatedness controls virulence rather than the pattern of transmission.

The Bull et al. (1991) study is important, in spite of these minor criticisms, because it shows the great potential in analysing parasite life history by experimental manipulation. In addition, the world of bacteria, viruses and plasmids is not a simplified model system, but rather a rich biological community that provides insight into the origin and evolution of parasites. Thus it would be useful to reexamine models of phage and plasmid life history in light of recent advances in the theory of parasite

virulence and to incorporate these studies into a broader theory of parasite biology.

GENOMIC CONFLICT

Recent work on genomic conflict is also strongly tied to problems of parasite virulence. This is a broad field (Werren et al. 1988; Hurst et al. 1992; Charlesworth et al. 1994). I limit myself to the topic of genetic diversity within hosts.

Eukaryotic cells maintain populations of symbionts. Some, such as mitochondria, obviously provide many benefits to the host cell. Others, such as cytoplasmic viruses or viruses integrated directly into the nuclear genome, may provide no benefits. Even the mitochondria, however, can face tradeoffs that favor virulent traits if balanced by increased competitive ability against other mitochondria within the cell. For example, a mitochondrial genotype that increases replication rate can spread within the cell even if the mutant contributes less to cellular fitness.

Hoekstra (1987) and Hurst and Hamilton (1992) have argued that lower genetic diversity among cytoplasmic elements is favored by the "host" because reduced diversity favors lower virulence. One way to reduce diversity is to prevent mixing of symbiotic lineages during sexual reproduction. Less mixing is achieved when gametes differ greatly in size (anisogamy), or the contribution of cytoplasmic elements is limited to only one of the two uniting gametes. Hurst and Hamilton (1992) argued that binary sexes, female and male, should be defined according to gametes that do and do not contribute cytoplasmic elements. They explain the evolution of binary sexes by noting that, with no mixing of cytoplasmic lineages, the hosts gain by reducing the level of competition and virulence expected from the symbionts.

The new genome theories and the recent parasite theories both emphasize the importance of genetic diversity within hosts. The models reviewed above suggest a simple way to link these theories. For both cytoplasmic elements and parasites, competitive traits with virulent side effects are favored according to the coefficient of relatedness within the host. Of course, many differences exist between genomic symbionts and infectious diseases such as malaria. Nonetheless, a common framework for parasite life history seems within reach.

Theories of genomic evolution share a simple elegance with the fundamental theories of virulence. However, the same cautions apply that I have discussed for virulence. Consider, for example, the evolution of transposition rate among transposons. More active transposition leads to a higher birth rate of the transposon and more copies in the genome. But transposition also has deleterious effects on the host (virulence), causing a higher death rate of the transposon. Transposition rates are generally favored to be lower in inbred than outbred species (Charlesworth and Langley 1986). In the language developed here, the relatedness of transposons within genomes increases with the degree of inbreeding. Groups of closely related "parasites" tend to lower their birth rate in order to reduce their virulence and negative effects on themselves and their neighbors.

Charlesworth and Charlesworth (1995) pointed out an interesting comparison between red-fruited and green-fruited species of *Lycopersicon*. The red-fruited species have a relatively high number of transposons per genome (Young et al. 1994) and appear to have a relatively higher rate of inbreeding (Rick 1984). This contradicts the prediction that high relatedness favors low transposition rate and low copy number per genome. Charlesworth and Charlesworth do not rule out the processes associated with relatedness, but point out that recombination between different genomic locations (ectopic exchange) may be a more powerful force or may act over a different time scale.

Chromosomal rearrangements produced by ectopic exchange appear to be a major aspect of virulence caused by transposons (Charlesworth et al. 1994). Evidence from *Drosophila* suggests that deleterious rearrangements are less frequent in chromosomal homozygotes than in heterozygotes, possibly because a heterozygous element at a given location is more likely to pair with an element elsewhere in the genome (Montgomery et al. 1991). If so, then outbred organisms will suffer higher virulence for a given number of transposons per genome than inbred species. This will produce a negative association between level of outbreeding and copy number.

In conclusion, the theories of parasite virulence should provide interesting hypotheses about genomic evolution. But simple, single-cause theories are no more likely to explain all aspects of a particular genomic interaction than for the detailed examples of parasite virulence discussed earlier.

EARLY EVOLUTION

Another way to broaden thinking about parasite traits is to consider the origin of parasites in early evolution. The first symbionts probably faced a complex mix of evolutionary pressures that favored some mutually beneficial traits and some traits that generated conflict among replicators. That complex mix continues today, with bacterial plasmids and mitochondria favored to benefit or harm the host in different circumstances.

The processes of conflict and cooperation that built early cells and created new evolutionary units are not fully understood (Maynard Smith 1988; Maynard Smith and Szathmáry 1995). I focus on a single model that illustrates many of the important problems of symbiosis.

In early evolution, the mutation rate per replicating molecule was probably quite high because complex repair enzymes had not yet evolved (Eigen 1971, 1992). The number of mutations per generation in each replicating molecule increases with the size of the molecule. Adaptive evolution can occur only when the rate of increase in fitness caused by selection is greater than the rate of decay in information caused by mutation. Thus mutation rate sets an upper limit, or "error threshold," on the size of replicating molecules. This creates a paradox because the size limit of early replicators without repair enzymes is too small to code for complex repair enzymes. Complex genomes cannot evolve without repair to lower mutation rates, and repair cannot evolve without complex genomes.

One solution is a "multispecies genome," with different replicators cooperating to catalyze the reproduction of genomic partners. With cooperation, molecule size can remain small while genome size increases. Repair enzymes could be produced cooperatively, allowing genome complexity to increase. Thus the puzzle is how did early replicators form mutualistic communities. Eigen and Schuster's (1979) hypercycle model was the first effort to address this problem.

In a hypercycle with two species, A and B, each species produces gene products that catalyze the replication of the other species. The pair of species, with A enhancing B's replication rate and B enhancing A's replication, is more efficient and competitive than either species reproducing alone. Thus a cooperative hypercycle can outcompete any individual replicators that do not take part in a cycle.

The problem with the hypercycle is that it can be invaded by parasites (Maynard Smith 1979; Bresch et al. 1980). Suppose that there is a population of As and Bs mixed together. Initially, there is a cooperative hypercycle, with all of the As aiding B's reproduction and, in return, all of the Bs catalyzing A's reproduction. Imagine a mutant of B that does not reciprocate and, by reducing time or energy devoted to reciprocating, can reproduce faster than other Bs. This parasitic mutant can outcompete the cooperative Bs because it gains the benefits of A's cooperation but does not bear any cost of returning benefits to A.

The stability of the hypercycle and the potential for parasitic invasion depend partly on kin or group selection (Szathmáry 1989a,b). Consider, for example, a large, mixed population of As and Bs. Focus on an individual B that devotes some of its energy to helping As. The altruism of this B individual causes it to receive more return benefits from the As because the altruism leads to more vigorous and numerous As. All B individuals share these return benefits, however, so there is no relative advantage to the original B donor. Put another way, the coefficient of relatedness is zero between the original donor and the recipients of return benefits. Since all Bs receive benefits from A, whether or not they contribute to helping the As, selfish, parasitic Bs can invade this system. This is similar to the general results for parasite virulence, in which low relatedness among parasites within hosts favors high virulence.

Several authors have proposed that parasitism can be reduced in hypercycles by confining the replicators to small, isolated populations bound within protocellular membranes

(Szathmáry 1989a,b). In these small populations the return benefits of aid to a partner species are likely to come back to the original donor or its close relatives. As expected, the optimum level of virulence declines as relatedness within cells increases or, put another way, the optimum level of cooperation rises as the relatedness increases within cells.

The similar role of population structure in models of protocellular cooperation and parasite virulence is clear. The next phase in models of early evolution is to consider how horizontal transfer of infectious replicators influences the evolution of genetic systems. Many aspects of parasite life history apply to this problem. One difference in these protocell models is that separate species may cooperate in a mutualistic cycle rather than in a strictly host-parasite interaction. Naturally, pairs of species that are transmitted together vertically are more likely to form cooperative communities than pairs of species that are mixed frequently by horizontal transmission. Yet, just as in the parasite models, too much emphasis on horizontal versus vertical transmission can be misleading (Frank 1994b). Instead, the key processes are statistical associations among genotypes—that is, coefficients of relatedness—and the binding of reproductive interests between different species. I discuss these processes in turn.

An asexual organism with pure vertical transmission is still prone to intense conflict among the symbionts that it contains. Mutations can, through time, accumulate within the lineage so that genetic variation of the symbionts within individual hosts is greater than the genetic differences between hosts. A low coefficient of relatedness within hosts promotes conflict rather than cooperation. The key factor determining the distribution of genetic variation, and thus relatedness, is the number of symbionts that pass from parent to offspring (Szathmáry and Demeter 1987). If each offspring is founded by a few symbionts sampled from the parent, then relatedness within hosts will be high and conflict will be minimized. Thus, as Maynard Smith (1988) pointed out, the fact that multicellular organisms reproduce through single cells may be explained by the need to create a genetic bottleneck in each generation, preventing rampant conflict among different genotypes within individuals. This is similar to the problem of parasite virulence with purely vertical transmission (see Figure 1).

Close relatedness aligns the reproductive interests of replicators and favors the evolution of a higher-level unit of selection. However, kin selection may have created opposing forces in early evolution. On the one hand, close relatedness integrates replicators into a cohesive cellular unit. On the other hand, kin selection favors the evolution of horizontal transmission (dispersal) between lineages in order to colonize new habitats and avoid competition with similar genotypes (Frank 1994a; Figure (5)). Thus, from the earliest phases of cooperative evolution, kin selection favored the origin of horizontal transmission and parasitism. The consequent mixing of lineages would break up the close relatedness that favors cooperation. Kin selection was both an integrating and a destructive force in early evolution, and was probably not sufficient to create higher-level units of selection (Frank 1995a).

Some form of binding of reproductive interests among replicators, such as physical linkage, may have been necessary for the evolution of efficient genomes (Maynard Smith and Szathmáry 1993, 1995; Frank 1995a, 1995b). The problem of linkage is how one starts with many different, separate replicator molecules and then evolves chromosomes with these replicators attached together as genes. Linkage on a chromosome causes synchrony of reproduction, forcing fully shared reproductive interests. In modern genomes, the great reproductive synchrony imposed by orderly meiosis is crucial for reducing the evolution of virulent genomic parasites. If transmission were vertical, but replicators competed within the host by differing rates of reproduction, then virulent parasites would be inevitable. When reproductive synchrony is imposed, then virulent parasites gain no advantage within a host. Thus, in the conceptual framework for parasite virulence, the problem of reproductive synchrony must be addressed and tied to the evolution of genomes. These interesting problems suggest many opportunities for future research.

CONCLUSION

Many observations from nature seemingly will have little connection to any simple theoretical framework, but that is an inevitable trait of any biological theory that seeks generality. One measure of success for a theory is whether it organizes the problem in a useful way, highlighting deviations that require further experiment and further thought. A second measure is whether the framework leads naturally to continued growth and connections to broader aspects of evolutionary theory, or eventually collapses into a series of ever more specialized descriptions of particular cases. By these measures, models of parasite virulence are an important component of current evolutionary thought.

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APPENDIX

The recursion in Equation (7)

$$F' = (1/k) + F[(k - 1)/k](1 - m)^2$$

was derived in the following way. The inbreeding coefficient, F, has many interpretations (Wright 1969), but the easiest way to build a recursion is by focusing on the probability of identity by descent. For my application, F is the probability that alleles from two parasites chosen from the same individual are identical by descent. All parasites are equally likely to be chosen, and sampling is done with replacement. Other definitions are: F' is the value of F after one generation, k is the number of parasites per individual, m is the migration rate, the fraction of the parasites in an individual derived from randomly chosen members of the population, and $(1 - m)$ is the fraction of parasites that come from the same donor host. The probability of identity by descent for pairs of parasites, F', can be derived by picking one parasite, and then considering the possible relations of that parasite to a second parasite within the same host. There are two components. First, the second parasite chosen may be the same one as the first, with probability $1/k$, because sampling is with replacement. Second, the other parasite may be different from the first, with probability $(k - 1)/k$. In this case, the pair of parasites is identical by descent if neither were immigrants, with probability $(1 - m)^2$, multiplied by the probability that pairs of parasites in the parent are identical by descent, F.

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