Evolution, 54(1), 2000, pp. 51–63

EVOLUTIONARY DYNAMICS OF PATHOGEN RESISTANCE AND TOLERANCE

B. A. ROY[1] AND J. W. KIRCHNER[2]
[1]*Geobotanical Institute, Swiss Federal Institute of Technology (ETH), Zürichbergstrasse 38, CH-8044 Zürich, Switzerland*
E-mail: roy@geobot.umnw.ethz.ch
[2]*Department of Geology and Geophysics, University of California, Berkeley, California 94720-4767*
E-mail: kirchner@seismo.berkeley.edu

Abstract.—Host organisms can respond to the threat of disease either through resistance defenses (which inhibit or limit infection) or through tolerance strategies (which do not limit infection, but reduce or offset its fitness consequences). Here we show that resistance and tolerance can have fundamentally different evolutionary outcomes, even when they have equivalent short-term benefit for the host. As a gene conferring disease resistance spreads through a population, the incidence of infection declines, reducing the fitness advantage of carrying the resistance gene. Thus genes conferring complete resistance cannot become fixed (i.e., universal) by selection in a host population, and diseases cannot be eliminated solely by natural selection for host resistance. By contrast, as a gene conferring disease tolerance spreads through a population, disease incidence rises, increasing the evolutionary advantage of carrying the tolerance gene. Therefore, any tolerance gene that can invade a host population will tend to be driven to fixation by selection. As predicted, field studies of diverse plant species infected by rust fungi confirm that resistance traits tend to be polymorphic and tolerance traits tend to be fixed. These observations suggest a new mechanism for the evolution of mutualism from parasitism, and they help to explain the ubiquity of disease.

Key words.—Cost of resistance, disease, herbivory, mutualism, parasitism, rust fungi, tolerance.

Received January 19, 1999. Accepted July 26, 1999.

Disease is ubiquitous in nature; by some estimates over half the organisms on Earth are pathogens or parasites (Price et al. 1986). Disease can structure natural communities (Dobson and Crawley 1994; Hiers and Evans 1997) and shape the course of evolution (May and Anderson 1983); it also causes immeasurable human suffering (Dobson and Carper 1996) and huge financial losses to agriculture (Klinkowski 1970). Hosts can cope with disease either through resistance defenses or through various tolerance strategies that permit them to survive and reproduce despite ongoing infection.

Resistance and tolerance are related but distinct concepts, and care must be taken to preserve the distinction between them. The terms ''resistance'' and ''tolerance'' have been used by different authors to refer to different things, and they have often been measured (and thus operationally defined) in ways that confuse the two concepts with each other. As a result, the literature on pathogen resistance and tolerance has become a semantic mine field (for a review of this problem see Clarke 1986). In keeping with the emerging consensus on resistance and tolerance (Clarke 1986; Fineblum and Rausher 1995; Strauss and Agrawal 1999), we hold to the following conceptual distinction: we use resistance to refer to traits that prevent infection or limit its extent, and we use tolerance to refer to traits that do not reduce or eliminate infection, but instead reduce or offset its fitness consequences. Thus, resistance and tolerance can both improve host fitness; resistance does so by reducing infection, whereas tolerance does so by reducing the fitness loss under infection.

Host resistance strategies include barriers to infection (such as skin, mucus, surface chemicals, and leaf hairs), mechanisms that rapidly clear infection (such as the immune response), and processes that limit the spread of infection within the host (such as localized cell death). All three types of resistance strategies inhibit the spread of infection by reducing the reproductive potential of the parasite. Barriers reduce the number of infected hosts; rapidly cleared infections reduce the duration of infection, and thus limit the time for pathogen reproduction; and mechanisms that limit spread limit the resources available for the pathogen.

Thus we use ''resistance'' to refer to host strategies that limit infection, and we note that any such strategies necessarily limit the pathogen's fitness. By contrast, tolerance traits do not limit infection itself, but reduce its fitness consequences for the host. Strategies that limit the extent of disease in an infected host are sometimes interpreted as helping the host ''tolerate'' infection, but these are normally termed resistance strategies (Clarke 1986) because they combat the pathogen by limiting its spread. This, in turn, reduces the pathogen's ability to reproduce.

Tolerance often involves some degree of compensation for disease damage. For example, plants can tolerate infection or herbivory by increasing the chlorophyll concentration in leaves, increasing the size of new leaves or the number of new branches, advancing the timing of bud break, delaying the senescence of infected tissue, and increasing nutrient uptake (Paige and Whitham 1987; Marquis 1992; Rosenthal and Welter 1995; Strauss and Agrawal 1999). Because both tolerance and resistance traits require reallocation of host resources, they tend to carry physiological costs (Simms and Rausher 1987; Herms and Mattson 1992; Simms and Triplett 1994; Bergelson and Purrington 1996; Mauricio et al. 1997).

Because the fitness consequences of disease are the lifetime exposure to infection (which resistance reduces) multiplied by the fitness loss when infection occurs (which tolerance reduces), resistance and tolerance can have similar direct effects on host fitness. Both strategies can be effective, but do they evolve in similar ways? Here we explore their evolutionary consequences by modeling the spread of resistance and tolerance traits in a host population.

Consider the evolutionary dynamics of a trait that confers complete resistance introduced into a host population (Fig. 1a,b,c). If the benefits of resistance outweigh its costs, the

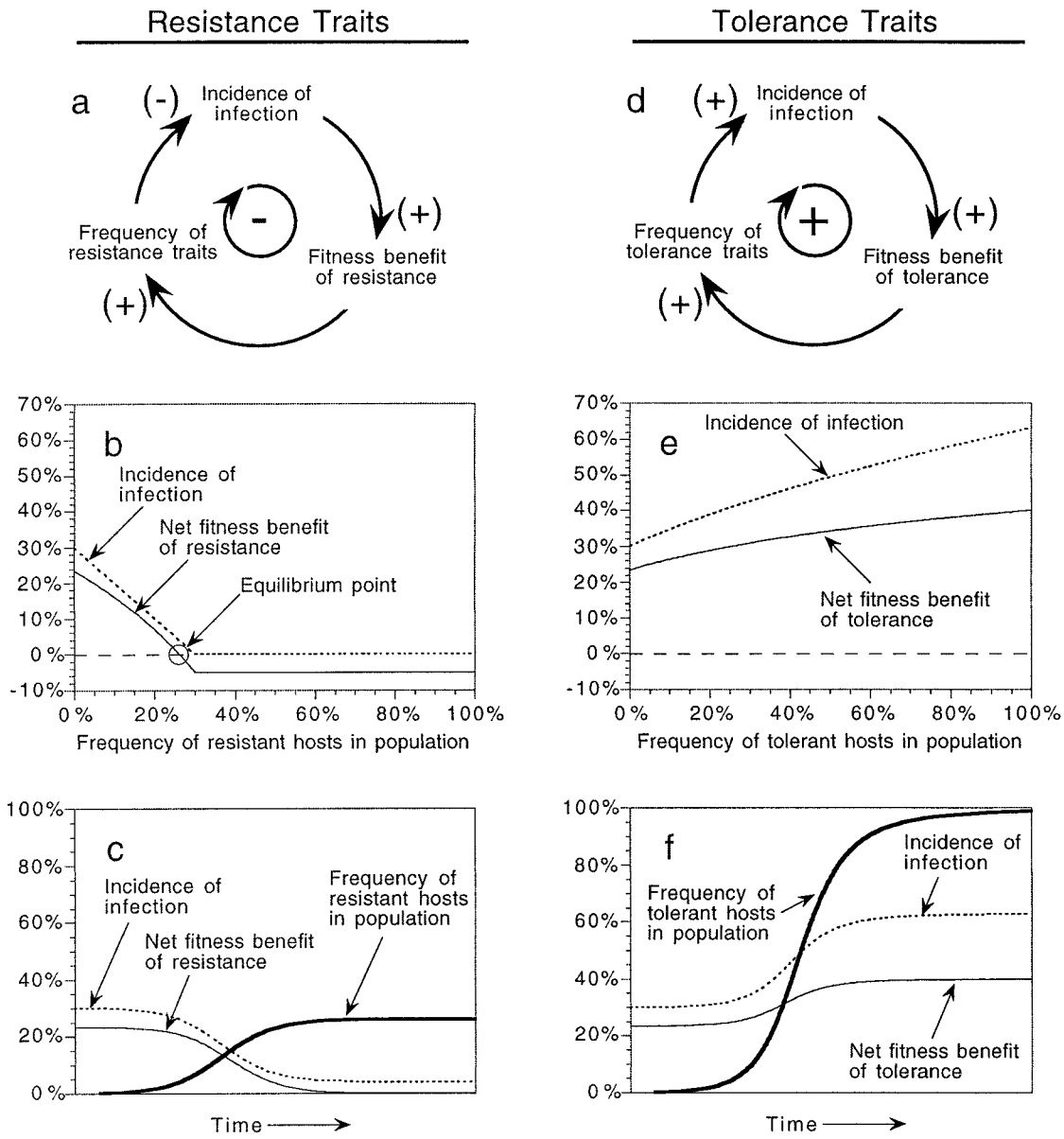


FIG. 1. Feedback mechanisms that govern the spread of resistance and tolerance traits. Arrows in causal loop diagrams (a,d) indicate causal linkages; signs of causal arrows indicate whether cause and effect move in the same (+) or opposite (−) directions. Net sign of each feedback loop, shown in its center, is determined by multiplying the signs of its individual linkages. Disease incidence (dotted lines) and fitness benefits of resistance or tolerance for the host (thin solid lines) decrease as resistant hosts become more prevalent (b), but increase as tolerant hosts become more prevalent (e). Thus, progressive loss of fitness advantage limits the spread of resistance (c), whereas a growing fitness advantage drives tolerance to fixation (f). Incidence of infection is I_{avg} from model equation (3), and fitness advantages are $(w_{RT} - w_o)/w_o$ (the percent difference in fitness between resistant/tolerant and reference hosts) is from model equations (9) and (10). Calculations assume that infection halves life span, and is initially present in 30% of a uniformly nonresistant, nontolerant population ($L_o = 0.5$, $I_{init} = 0.3$). Host traits confer complete resistance ($R = 1$, $T = 0$) or complete tolerance ($R = 0$, $T = 1$), at a fitness cost of 5% ($C = 0.05$).

proportion of resistant hosts in the population will increase through time. As more of the host population becomes resistant to infection, the overall incidence of infection in the population will decline, thus lowering the risk of infection for nonresistant individuals as well. As the risk of infection declines, resistant individuals will gradually lose their fitness advantage over nonresistant individuals. At some point, the risk of infection will be so low that the benefits of resistance will no longer be worth its costs, and the resistance trait will stop spreading. This steady state will be reached before resistance has become fixed (i.e., universal in the host population) and before the risk of infection has been entirely eliminated. For the resistance trait to continue to spread, the risk of infection must be great enough that the benefits of resistance outweigh its costs. For this reason, disease cannot be eliminated by natural selection for host resistance traits.

Now, by contrast, consider the evolutionary dynamics of a trait that confers complete tolerance, introduced into a host

population (Fig. 1d,e,f). If the benefits of tolerance outweigh the costs, tolerant hosts will have a fitness advantage over nontolerant hosts and the tolerance trait will become more prevalent in the host population. As more of the host population becomes tolerant to infection, the overall incidence of infection in the population will increase because tolerance prolongs the survival of infected hosts, and thus of their pathogens, heightening the risk of infection for tolerant and nontolerant hosts alike. As the risk of infection grows, so does the fitness advantage of tolerant hosts over nontolerant hosts, and the tolerance trait will continue to spread in the population until it becomes fixed.

Thus, even though resistance and tolerance may have equivalent short-term benefits for individual hosts, their evolutionary dynamics are fundamentally different because they reshape the selection regime in opposite ways. The negative feedback between the prevalence of resistant hosts and their fitness advantage (Fig. 1a,b) impedes the spread of resistance genes in the host population (Fig. 1c). By contrast, the positive feedback between the prevalence of tolerant hosts and their fitness advantage (Fig. 1d,e) accelerates the spread of tolerance genes (Fig. 1f). The resistance trait converges toward a polymorphic equilibrium, whereas the tolerance trait goes to fixation.

The negative feedback (Fig. 1a) that limits the spread of resistance traits will occur whenever: (1) infection decreases host fitness, which is the definition of disease itself; (2) resistance decreases the risk of infection, which is the definition of resistance; and (3) the risk of infection increases with increasing incidence of disease in the population. Given this negative feedback, genes conferring complete resistance cannot become fixed by natural selection, as long as there is some cost of resistance. The positive feedback (Fig. 1d) that drives tolerance traits to fixation will occur whenever: (1) infection decreases fitness in nontolerant hosts (the definition of disease); (2) tolerance decreases the fitness consequences of infection (the definition of tolerance); (3) the risk of infection increases with increasing disease incidence in the population; and (4) disease incidence increases with the spread of tolerance in the host population. Thus, the behaviors shown in Figure 1 should be observed under nonrestrictive conditions.

In the rest of this paper we develop and explore the implications of these concepts in quantitative terms. The feedback mechanisms driving the patterns of behavior shown in Figure 1 do not depend on the particular mathematical model outlined below. However, that model allows us to describe how the evolutionary fate of resistance and tolerance traits depend on properties of the host-pathogen system, such as the pathogen's virulence and its initial incidence of infection. Although the concepts that we develop here should broadly apply to both plant and animal hosts, our examples will come from the plant literature because we are more personally familiar with the biology of plant-pathogen systems, and because these systems present several clear examples of host tolerance to widespread, persistent infection. Although we explicitly model host responses to pathogens, our results also apply to specialist herbivores, including many important agricultural pests (cf. Tiffin's [2000] recent work that draws, in part, on the analysis presented here).

Modeling the Fitness Consequences of Resistance and Tolerance Traits

Here we present a simple model describing the fitness implications of resistance and tolerance to pathogens. This analysis is not meant to capture the biological details of any particular host-pathogen system; it is instead designed to provide a general framework for discussing resistance, tolerance, and their evolutionary consequences in quantitative terms. The results and discussion can be read without a mastery of the mathematical details, which are presented here to document our analysis. A complete list of symbols is given in Table 1.

Incidence of Infection

We model an endemic pathogen that causes a permanent systemic disease in a long-lived host. Examples of such infections include syphilis and AIDS, as well as many fungal pathogens, such as rusts and smuts, that afflict perennial plants (Jarosz and Davelos 1995). Our analysis can be readily extended to include host recovery from disease, with or without acquired immunity. For simplicity of explanation, we present the model as if the hosts resist disease by inhibiting pathogen entry (or by rapidly clearing the pathogen before disease is established). However, resistance that inhibits the spread of infection within hosts should have functionally equivalent consequences in our model; that is, resistance that halves the number of infected hosts, and resistance that halves the extent to which each host is infected, should have equivalent effects.

We assume the disease is transmitted only horizontally; that is, all offspring are born healthy. In our analysis, infection shortens host life span (and thus decreases host fitness) by a fraction L_i (which may vary between the host strains, depending on their degree of disease tolerance). We denote the mean life span of an uninfected host by τ and the mean life span of an infected host by $\tau_i^* = \tau(1 - L_i)$.

In our analysis, the total size of the host population is assumed to be fixed by external constraints, such as the availability of light or essential nutrients. As a result, the incidence of infection and the prevalence of resistance/tolerance can be completely specified as fractions of the host population. This is appropriate because we are concerned with changes in host phenotype frequencies, not the host's population dynamics. The pathogen cannot survive without hosts, so its population need not be modeled independently of the infected host population.

Our host population consists of only two strains (phenotypes): a reference strain (denoted ''*o*'') and a strain with higher resistance and/or tolerance to pathogen infection (denoted ''*RT*''). Because both host strains can infect each other, the rate of new infections is proportional to the average incidence of infection across both host strains I_{avg} (representing the supply of infectious propagules), the uninfected population X (which supplies sites for new infections), and a transmission coefficient β (which combines the effects of population density, pathogen infectiousness, and host susceptibility). We assume that over evolutionary time scales, the rate of infection is in equilibrium with the death of infected hosts (Y/τ^*, where Y is the infected population, and τ^* is the

TABLE 1. Table of symbols.

Symbol	Definition	Defining equation (or first use)
i	Subscript placeholder for host strains o or RT	(2)
o	Subscript for reference strain	(1)
RT	Subscript for resistant/tolerant strain	(1)
a	Host reproduction rate	(5)
β	Pathogen transmission coefficient	(1)
C	Cost of host resistance/tolerance (fraction reduction in a)	(8)
f_i	Fraction of hosts in ith strain	(3)
I	Incidence of infection (fraction of hosts infected)	(1)
I_{avg}	Overall incidence of infection across both host strains (fraction infected)	(1)
I_{init}	Initial incidence of infection (in reference population)	(15)
τ	Mean life span of uninfected hosts	(4)
τ^*	Mean life span of infected hosts	(1)
L	Fraction decrease in mean life span when infected	(5)
e	Lifetime risk of infection	(4)
R	Host resistance to infection (fraction reduction in β)	(6)
T	Host tolerance of infection (fraction reduction in L)	(7)
w	Host fitness	(5)
X	Uninfected host population	(1)
Y	Infected host population	(1)

life span of infected hosts). Thus, for the two host strains, these equilibria are:

$$\beta_o X_o I_{avg} = Y_o/\tau_o^* \quad \text{and} \quad \beta_{RT} X_{RT} I_{avg} = Y_{RT}/\tau_{RT}^*, \qquad (1)$$

where o and RT represent the reference strain and the resistant/tolerant strain (we will also use i as a subscript that can stand for either host strain). Defining the incidence of infection I_i as the fraction of hosts in the i^{th} strain that are infected, we rewrite (1) as:

$$\beta_i(1 - I_i)I_{avg} = I_i/\tau_i^* \quad \text{or} \quad I_i = \frac{\beta_i \tau_i^* I_{avg}}{1 + \beta_i \tau_i^* I_{avg}}. \qquad (2)$$

If we define the fraction of hosts (both infected and uninfected) in strain i as f_i, we can rewrite the overall incidence of infection I_{avg} in terms of the incidences of infection I_i in the individual strains:

$$I_{avg} = f_o I_o + f_{RT} I_{RT} = \sum f_i I_i. \qquad (3)$$

The incidence of infection I_i in each strain and the overall incidence of infection I_{avg} are interdependent, but they can be jointly determined by solving equations (2) and (3) as a quadratic. For more than two host strains, the equations can be solved iteratively; they converge rapidly.

The lifetime risk of infection for an individual in the ith host strain is determined by the relationship between the rate of infection and the mortality rate of uninfected hosts:

$$e_i = \frac{\beta_i I_{avg}}{\frac{1}{\tau} + \beta_i I_{avg}} = \frac{\beta_i \tau I_{avg}}{1 + \beta_i \tau I_{avg}}, \qquad (4)$$

where τ (here without the asterisk) denotes the uninfected life span, which we assume is the same for both host strains. Because infection shortens life span, the lifetime risk of infection (e_i) will be higher than the incidence of infection (I_i), which is the fraction of hosts that, at any given moment, are sick but still alive to be counted (and to spread infection).

Equations (1–4) assume that the host population evolves (in response to the prevailing incidence of disease) much more slowly than the incidence of disease responds (to the frequency of resistance or tolerance in the host population). This makes sense for endemic diseases in long-lived hosts, because hosts typically evolve over time scales of many generations, whereas the incidence of disease can adjust over much shorter time scales. We have taken this natural decoupling of time scales to its theoretical limit by expressing the incidence of infection as an implicit function of the host phenotype frequencies.

The fitness benefit of resistance or tolerance depends on the fitness consequences of infection. Here, we assume that disease reduces host longevity (and thus decreases host fitness) by a fraction L_i. We denote the longevity of an uninfected host by τ, and thus $\tau_i^* = \tau(1 - L_i)$ is the longevity of an infected host. The overall fitness of the ith host strain is thus:

$$w_i = a_i \tau(1 - e_i) + a_i \tau_i^* e_i = a_i \tau(1 - e_i L_i), \qquad (5)$$

where a_i is the reproduction rate of the ith host strain and e_i is the lifetime risk of infection (or exposure to infection) for that host strain. Equation (5) shows (as intuition would suggest) that the average fitness consequence of infection is the lifetime risk of infection (e_i) multiplied by the fitness loss when infection occurs (L_i).

Resistance and Tolerance

This mathematical formalism provides a natural framework for quantifying resistance and tolerance. As we explained above, we use ''resistance'' to denote traits that inhibit infection (thus reducing the risk of infection, e_i, in eq. 5), and we use ''tolerance'' to denote traits that limit the fitness consequences of infection if it occurs (thus reducing the fitness loss under infection, L_i, in eq. 5). Because the fitness consequences of infection depend on both e_i and L_i, resistance and tolerance can have equivalent short-term fitness benefits for the host.

All measures of resistance and tolerance are necessarily relative. Because rates of infection are jointly determined by

pathogen infectiousness and host resistance, levels of host resistance cannot be measured on an absolute scale. One can only measure relative levels of resistance, by comparing rates of infection among different host strains under comparable levels of pathogen attack. Likewise, because the fitness consequences of infection (if it occurs) are jointly determined by host tolerance and pathogen lethality, one can only measure relative levels of host tolerance by comparing the fitness of different host strains under comparable levels of active infection.

In our model, the reference host strain provides an obvious zero-point for our relative resistance and tolerance scales because we seek to compare the fitness of this reference strain and one with higher resistance and/or tolerance (the *RT* strain). For the purposes of our model, we define resistance (R) as the fraction by which the pathogen transmission coefficient β is reduced in the resistant/tolerant strain compared to the reference host strain:

$$\beta_{RT} = \beta_o(1 - R). \tag{6}$$

R can reflect both the reduction of host-to-host transmission and the inhibition of pathogen spread within individual hosts. We define tolerance (T) as the fraction by which the fitness impact of infection (L) is reduced in the resistant/tolerant strain compared to the reference host strain:

$$L_{RT} = L_o(1 - T). \tag{7}$$

Both resistance and tolerance are therefore defined on a scale from zero (β or L equal to the reference host strain) to one ($R = 1$ implies no chance of infection, and $T = 1$ implies that infected hosts have no loss of fitness).

Because the fitness consequence of infection is the risk of infection multiplied by the fitness loss under infection (see eq. 5), complete resistance makes tolerance unnecessary, and complete tolerance makes resistance unnecessary. From the host's perspective, the fitness loss under infection is irrelevant if the risk of infection is zero, and conversely, the risk of infection is irrelevant if the fitness loss under infection is zero. If resistance and tolerance both have costs, their mutual redundancy will give hosts with either high resistance or high tolerance an advantage over hosts that exhibit both of these traits together. Thus, one should expect to find a negative correlation between levels of resistance and levels of tolerance, and empirical studies have shown that this is the case. Although this pattern can arise from genetic or physiological trade-offs between resistance and tolerance traits (Simms and Triplett 1994; Fineblum and Rausher 1995; Stowe 1998), it can also arise simply from their mutual redundancy (Van der Meijden et al. 1988).

Note that we define our resistance and tolerance scales such that the reference host strain has resistance of zero and tolerance of zero. This does not mean that the reference strain exhibits no resistance or tolerance. Instead, it means that its level of resistance is already reflected in the pathogen transmission coefficient, β_o, and its level of tolerance is already reflected in the fitness loss, L_o. To the extent that the reference strain can resist infection, β_o will be smaller than it would have been otherwise, and to the extent that it can tolerate infection, L_o will be smaller than it would have been otherwise. The reference strain serves to anchor the resistance and tolerance scales; thus, the biological significance of R and T must be evaluated in comparison to the β_o and L_o of the reference strain.

We assume that resistant/tolerant hosts incur a fitness cost (C) associated with their increased level of resistance and/or tolerance. We model this cost as the fraction by which the reproduction rate of resistant/tolerant hosts is reduced, compared to the reference strain:

$$a_{RT} = a_o(1 - C). \tag{8}$$

Combining equations (4) and (5–8), we can write the fitness of the reference strain as:

$$w_o = a_o\tau(1 - e_oL_o) = a_o\tau\left(1 - \frac{\beta_o\tau I_{avg}}{1 + \beta_o\tau I_{avg}}L_o\right) \tag{9}$$

and the fitness of the resistant/tolerant strain as:

$$w_{RT} = a_{RT}\tau(1 - e_{RT}L_{RT}) = a_{RT}\tau\left(1 - \frac{\beta_{RT}\tau I_{avg}}{1 + \beta_{RT}\tau I_{avg}}L_{RT}\right)$$

$$= a_o(1 - C)\tau\left(1 - \frac{(1 - R)\beta_o\tau I_{avg}}{1 + (1 - R)\beta_o\tau I_{avg}}L_o(1 - T)\right). \tag{10}$$

The frequency of the resistance/tolerance trait (f_{RT}) will affect the incidence of infection and, thus, the fitness of both host strains. The relative fitnesses of the two host strains, in turn, will determine how f_{RT} will change through time. How fast this change occurs will depend on the size of the fitness difference and on the host genetics. However, the details of the host genetics affect only the rate of convergence toward steady state, not the direction of selection or the equilibrium phenotype frequencies themselves, which are the main objective of our analysis. Evolutionary equilibrium will be reached when the fitnesses of the ordinary and resistant/tolerant hosts are equal. The equilibrium phenotype frequencies can be calculated without iterative search methods, as follows. First, set w_o and w_{RT} (eqs. 9 and 10) equal to each other, then solve the resulting (rather cluttered) quadratic for the incidence of infection I_{avg} at which the two host strains would have equal fitness. Next use equation (2) to calculate the incidence of infection in the two host strains, and finally solve equation (3) for the value of f_{RT} at which equilibrium occurs.

The model is fully specified by five parameters: three describing the resistance/tolerance trait (the level of resistance R, the level of tolerance T, and the fitness cost C of expressing the trait), and two characterizing the host-pathogen system (the fitness loss, L_o, under infection and the initial level of infection, I_{init}, in the reference strain). In the Appendix we describe how these parameters could potentially be measured, and how they can be used to derive the other terms in equations (1–10).

Results and Discussion

The model outlined above yields several insights concerning the evolution of resistance and tolerance in host populations. For brevity and clarity, we give these observations individually in italics, followed by explanations.

Spread of Resistance and Tolerance Traits

The direct effects of resistance and tolerance on host fitness can be comparable, and even redundant, but their evolutionary

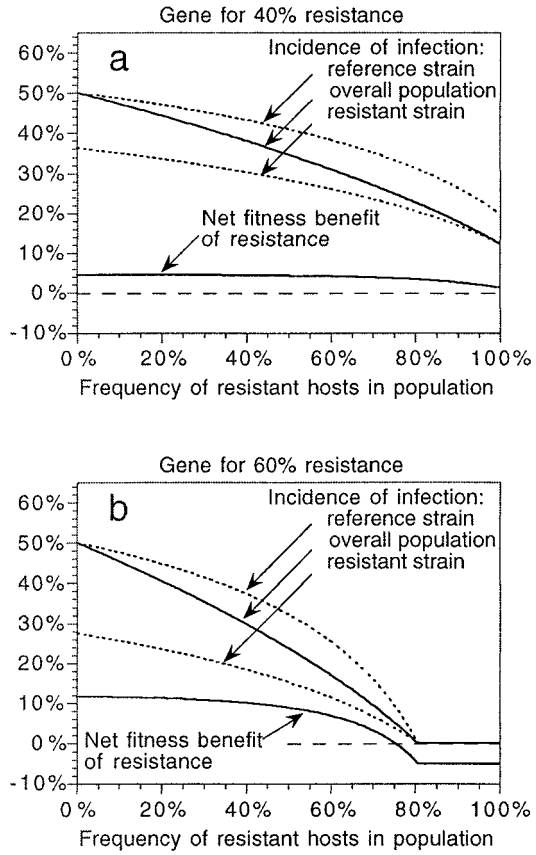


FIG. 2. Effect of the frequency of resistant hosts on their relative fitness, and on disease incidence, for traits conferring incomplete resistance. In (a), the resistant strain's level of resistance is low enough that the incidence of disease (and thus the fitness benefit of resistance) remains significant, even if every host belongs to the resistant strain. Thus, this resistance trait could become fixed by selection. In (b), the resistant strain's level of resistance is somewhat higher than in (a), and the incidence of disease (and the fitness benefit of resistance) would vanish while the host population was still polymorphic. Model parameters are $I_{init} = 0.5$, $L_o = 0.5$, $C = 0.05$, $T = 0$, and either $R = 0.4$ (a) or $R = 0.6$ (b).

dynamics are fundamentally different because they alter the incidence of infection in opposite ways. The spread of resistance traits in a host population decreases the incidence of disease and thus weakens selection for resistance (Figs. 1a–c, 2). By contrast, the spread of tolerance in a host population increases the incidence of disease and thus increases the fitness value of tolerance traits (Fig. 1d–f). Thus, negative feedback limits the spread of resistance traits, whereas positive feedback reinforces the spread of tolerance traits.

As resistance traits spread in a host population, the fitness advantage of resistance vanishes before the disease itself does (Figs. 1b, 2). *Thus, infectious diseases cannot be eliminated by natural selection for host resistance because infection must be present for resistance to be advantageous (and thus favored by selection).* As the frequency of resistance in the host population increases, the overall incidence of infection declines and so does the difference in infection rates between the two host strains (Fig. 2). Can resistance become widespread enough to extinguish infection? Extinguishing infection requires that during its lifetime, the average infected host can spread infection to less than one other host:

$$f_o\beta_o\tau_o^* + f_{RT}\beta_{RT}\tau_{RT}^* < 1 \tag{11}$$

(Anderson and May 1991). This condition could be met if resistant hosts were sufficiently resistant and sufficiently prevalent in the host population. However, this cannot occur through selection alone, because as the incidence of infection nears the vanishing point, the difference between the two host strains, and thus the fitness advantage of the resistant strain, vanishes as well (Fig. 2).

Resistance will continue to spread through the host population only if it reduces the risk of infection enough to be worth its cost. From equations (4, 9, 10) one can show that this condition is met when:

$$\frac{(e_o - e_{RT})L_o}{1 - e_{RT}L_o} > C. \tag{12}$$

If the incidence of infection is small, as it must be if it is on the verge of being eliminated, $e_{RT}L_o \ll 1$, and equation (12) becomes:

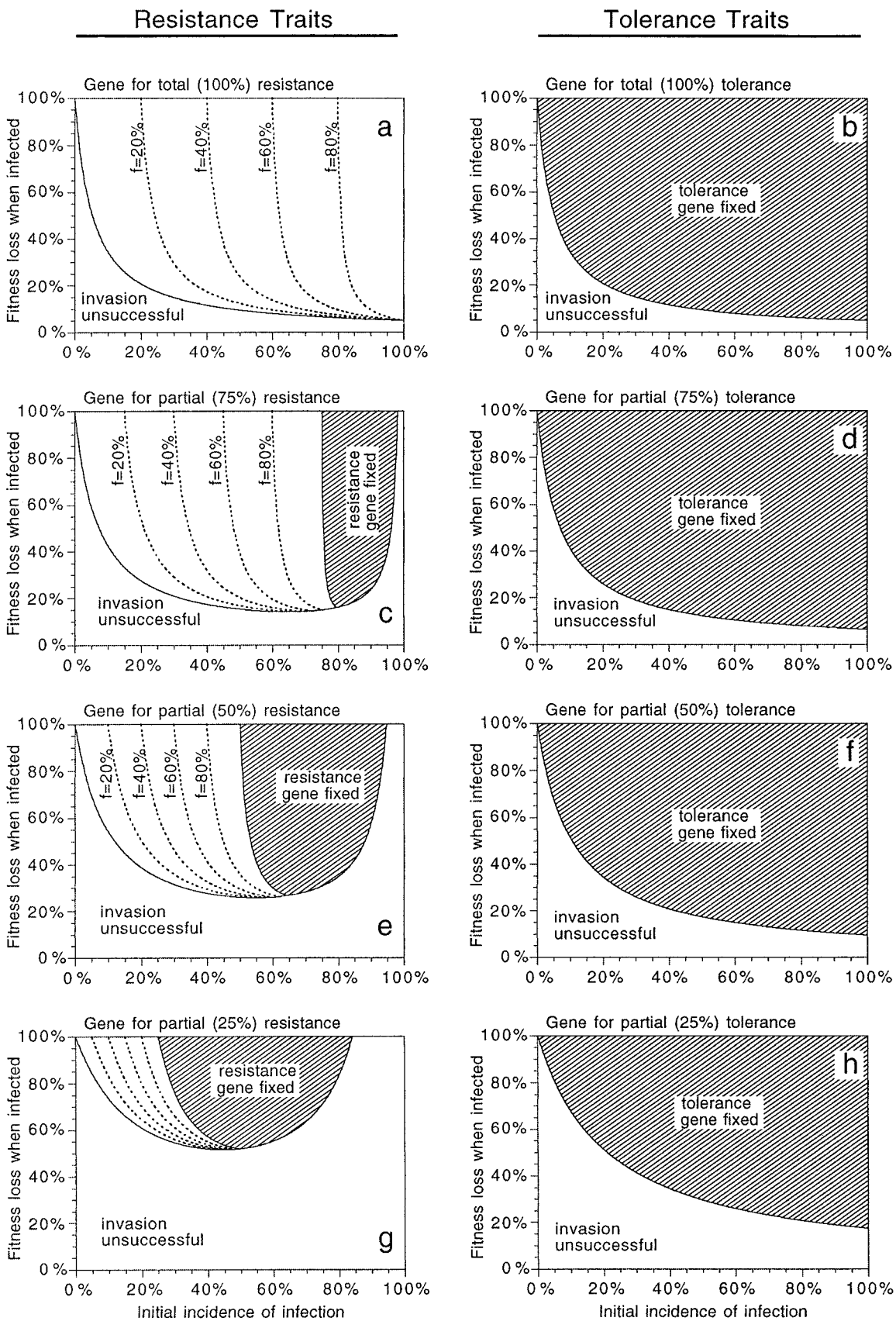
$$e_oL_oR > C. \tag{13}$$

Equation (13) makes good intuitive sense; it says that when the incidence of infection is small, the fitness benefit of resistance is roughly proportional to the fitness loss due to infection (L_o), the risk of infection (e_o), and the degree of resistance (R). Equation (13) clearly shows that before disease is eliminated from the host population (i.e., before e_o is driven to zero), the benefits of resistance will sink below the costs (as long as those costs are nonzero) and selection will no longer favor the resistant host strain. This mechanism is sufficient to explain why disease is so widespread in nature, even without coevolutionary ''Red Queen'' processes (Clay and Kover 1996; Lively 1996), although these may also be present. Even if host resistance traits could potentially wipe out a disease, selection cannot make them widespread enough to do so.

Genes conferring complete resistance cannot become fixed in a host population by selection alone (Fig. 3a), and genes for partial resistance can only become fixed under particular combinations of pathogen infectiousness and virulence (Fig.

→

FIG. 3. Equilibrium frequencies, f_{RT}, of traits conferring different levels of resistance or tolerance, as a function of pathogen infectiousness and pathogen virulence. Hatched areas indicate conditions where the equilibrium frequency is 100% (fixation). Dashed contours show resistance trait frequencies in polymorphic equilibria. No such polymorphic equilibria exist for tolerance traits; all conditions that permit invasion lead to fixation. Solid lines indicate invasion thresholds, below which tolerant or resistant hosts have a net disadvantage. Horizontal axis for all panels is the initial incidence of infection in a uniform population of the reference strain (I_{init} in model eq. A1); vertical axis is the fitness loss caused by infection in nontolerant individuals (L_o in model eq. 5). Levels of resistance and tolerance, which are specified above each panel, are R and T in equations (6) and (7), respectively; all traits carry a fitness cost (C) of 5%.


Resistance Traits
Tolerance Traits
Gene for total (100%) resistance
Gene for total (100%) tolerance
Gene for partial (75%) resistance
Gene for partial (75%) tolerance
Gene for partial (50%) resistance
Gene for partial (50%) tolerance
Gene for partial (25%) resistance
Gene for partial (25%) tolerance
Fitness loss when infected
Initial incidence of infection
0 %
20%
40%
60%
80%
100%
f=20%
f=40%
f=60%
f=80%
a
b
c
d
e
f
g
h
invasion unsuccessful
tolerance gene fixed
resistance gene fixed

3c,e,g). As we have shown above, infection must exist for selection to favor more resistant hosts. Therefore, the equilibrium frequency of host resistance cannot exceed the frequency that would eliminate infection. From equation (6) and the criterion in equation (11), one sees that for infection to persist, the frequency of resistant hosts must be:

$$f_{RT} < \frac{1 - \frac{1}{\beta_o \tau (1 - L_o)}}{R}, \tag{14}$$

if $T = 0$ and thus $L_{RT} = L_o$. Using equation (A1), this can be further simplified to:

$$f_{RT} < \frac{I_{init}}{R}, \tag{15}$$

which indicates that a resistance trait cannot go to fixation if the level of resistance it confers (R) is greater than the initial incidence of infection in the reference strain (I_{init}). Because $I_{init} < 1$, genes conferring complete resistance ($R = 1$) cannot be driven to fixation by selection. Note also that the equilibrium frequency f_{RT} will be less than one whenever $I_{init} < R$, even if $R < 1$ (i.e., the gene confers incomplete resistance). In fact, the constraint on f_{RT} is stricter than equations (14) and (15) suggest because resistance traits will stop spreading before the incidence of infection is driven all the way to zero. Instead, as equation (12) shows, they will stop spreading when:

$$I_{avg} \approx \frac{C}{\beta_o \tau L_o R} \quad \text{or, equivalently,}$$

$$I_{avg} \approx \frac{C}{R} \frac{1 - L_o}{L_o} (1 - I_{init}). \tag{16}$$

This condition will be achieved at a lower frequency of resistance than that which would eliminate infection completely.

In Figure 3 we have mapped out the equilibrium frequencies of resistance and tolerance traits for all possible degrees of pathogen infectiousness and virulence (represented by the initial incidence I_{init} and fitness consequences L_o of infection). As the contour lines in Figure 3 show, resistance traits are predominantly polymorphic, with fixation expected only for incomplete resistance, and only under conditions of high virulence and relatively high infectiousness. Figure 3 illustrates the generality of the behavior shown in Figures 1 and 2.

Partial resistance genes cannot invade when pathogen infectiousness is very high (right edge of Fig. 3c,e,g), because such conditions are so saturated with infection opportunities that partial resistance has too little effect on the risk of infection. Invasion is possible in the upper left corner of each panel, because if infection severely curtails longevity (and thus there are few infected individuals alive to be counted) the incidence of infection can be low even though the lifetime risk of infection is high (and disease is thus a substantial threat to host fitness).

Using a variety of models, others have previously shown that selection cannot fix genes that confer complete resistance, when resistance carries a cost (Gillespie 1975; Leonard and Czochor 1980; May and Anderson 1983). Our work extends this result, by demonstrating that under a broad range of conditions, even genes conferring *incomplete* resistance cannot become fixed by natural selection alone (although genetic drift could lead to fixation in small populations).

Any tolerance gene that can invade a host population should be driven to fixation by selection (Fig. 3b,d,f,h). From equations (4, 9, 10), one can show that the fitness benefits of tolerance outweigh its costs when:

$$\frac{e_o L_o T}{1 - e_o L_o (1 - T)} > C. \tag{17}$$

The benefits of tolerance are roughly proportional to the level of tolerance, T, the fitness loss under infection, L_o, and the lifetime risk of infection, e_o (which is the same for tolerant and nontolerant hosts, assuming they have the same level of resistance). As tolerance traits spread in the host population, the risk of infection (e_o) rises, thus increasing the fitness benefit of tolerance. Consequently, a tolerance trait that is advantageous at $f_{RT} = 0$ will be even more advantageous at $f_{RT} = 1$. As a result, any tolerance trait that confers a net benefit, and thus can successfully invade a host population, should be carried to fixation by natural selection (Fig. 3).

If a particular tolerance trait does not extend the life span of infected hosts, but instead accelerates host reproduction, the incidence of infection (and thus the fitness benefit of tolerance) will remain constant as that trait spreads through the host population. Such a tolerance trait would still be driven to fixation, but somewhat more slowly without the boost provided by positive feedback.

Frequency of Resistance and Tolerance Traits in Natural Populations

Studies of rust diseases in natural populations (Table 2) suggest that, as predicted, resistance traits are generally more polymorphic than tolerance traits. Table 2 summarizes the results from 11 studies that quantified rust fungus disease incidence and fitness consequences in natural plant populations. To the best of our knowledge, these studies comprise the entire published literature of rust disease in natural populations from which one can extract information on both fitness consequences and disease incidence. In roughly half the populations studied, the fitness consequences of infection were very low, despite levels of disease incidence ranging from 50% to 100%. For example, in one Great Basin shrub community (cases 1, 3, 4, and 6–8 in Table 2), three dominant species sustained 85–100% infection with rust fungi over a two-year period, with little or no effect on survival or flowering (Roy et al. 1997; B. A. Roy, J. W. Kirchner, C. Christian, and L. Rose, unpubl. ms.). This pattern—widespread disease with little or no fitness consequences—can be interpreted as indicating that high levels of tolerance must be nearly universal in the host populations.

The same observations can also be interpreted as indicating benignness (avirulence) on the part of the pathogen, rather than tolerance on the part of the host. Pathogen avirulence should be selected for whenever transmission depends on low virulence, such as when host density is low (Bull 1994; Lenski and May 1994). Conversely, pathogen avirulence should be selected against when different strains are competing with-

TABLE 2. Disease incidence and fitness consequences of infection for a variety of rust fungus–host systems. Infection types: l, localized infections; s, systemic infections. References: (1) Roy et al. 1997; (2) Wennström et al. 1995; (3) Alexander 1991; (4) Davelos et al. 1996; (5) Jarosz and Davelos 1995; (6) Frantzen 1994; (7) Watson and Keogh 1980; (8) Parker 1987; (9) Roy 1993; (10) Roy and Bierzychudek 1993; (11) Wennström and Ericson 1991.

Case	Disease incidence %	% decrease in repro-duction	% decrease in survival	% decrease in fitness[1]	Host	Pathogen	Infection type	Site name	Other information	Year	Source
1	100.0	0[2]	0[2]	0	*Stephanomeria spinosa*	*Puccinia hieraci*[7]	s, l	Ft. Sage	avg. of 5 plots	1995	1, unpubl.
2	97.2	4.0[3]	0[3]	4.0	*Lactuca siberica*	*Puccinia minusensis*	s, l	Långed		1989	2
3	97.1	0	0	0	*Erigonum microthecum*	*Uromyces intricatus*[7]	s, l	Ft. Sage	avg. of 5 plots	1995	1, unpubl.
4	96.9	5	0	5	*Balsamorhiza sagittata*	*Puccinia balsamorhizae*	s, l	Ft. Sage	avg. of 5 plots	1995	1, unpubl.
5	95.0	0[2]	0[2]	0	*Helianthus annuus*	*Puccinia helianthi*[1]	s, l				3, pers. comm.
6	90.3	0[2]	0[2]	0	*Stephanomeria spinosa*	*Puccinia hieraci*[7]	s, l	Ft. Sage	avg. of 5 plots	1996	1, unpubl.
7	89.3	0[2]	0[2]	0	*Balsamorhiza sagittata*	*Puccinia balsamorhizae*	s, l	Ft. Sage	avg. of 5 plots	1996	1, unpubl.
8	84.9	7.0	0	7.0	*Erigonum microthecum*	*Uromyces intricatus*[7]	s, l	Ft. Sage	avg. of 5 plots	1996	1, unpubl.
9	77.7	4.0[3]	0[3]	0	*Lactuca siberica*	*Puccinia minusensis*[7]	s, l	Långed		1990	2
10	77.0	0	0	0	*Spartina spectinata*	*P. seymouriana* and *P. sparganiodes*[6,8]	1	Netherlands	avg. of 5 nearby pops.	1992	4, 5
11	68.6	4.0[3]	0[3]	4.0	*Lactuca siberica*	*Puccinia minusensis*[7]	s, l	Långed		1992	2
12	65.3	4.0[3]	0[3]	4.0	*Lactuca siberica*	*Puccinia minusensis*[7]	s, l	Långed		1991	2
13	62.9[9]	0[2]	0[2]	0	*Circium arvense*	*Puccinia punctiformis*[7]	1	Netherlands	avg. of 4 nearby pops.	1990	6, 7
14	58.1[9]	0[2]	0[2]	0	*Circium arvense*	*Puccinia punctiformis*[7]	1	Netherlands	avg. of 4 nearby pops.	1989	6, 7
15	27.8	79.0	—	≥ 79.0	*Arisaema triphyllum*	*Uromyces ari-triphylli*[7]	s, l	Thorn Creek		1985	8
16	16.8	98.7	38.5	99.2	*Arabis holboellii*	*Puccinia monoica*[8]	s	Cold Creek		1990	9, 10
17	10.9	98.7[4]	38.5[4]	99.2	*Arabis holboellii*	*Puccinia monoica*[8]	s	Taylor River		1990	9, 10
18	9.5	100.0	0	100.0	*Pulsatilla pratensis*	*Puccinia pulsatillae*[7]	s	Gårdby	perm. plot	1989	11
19	7.6	98.7	38.5	99.2	*Arabis holboellii*	*Puccinia monoica*[8]	s	Cement Creek		1990	9, 10
20	7.5	100.0	0	100.0	*Pulsatilla pratensis*	*Puccinia pulsatillae*[7]	s	Gårdby	perm. plot	1988	11
21	7.4[9]	96.1[5]	90.0	99.6	*Circium arvense*	*Puccinia punctiformis*[7]	s	Netherlands	avg. of 4 nearby pops.	1990	6, 7
22	5.0	100.0	1.5	100.0	*Arabis holboellii*	*Puccinia thlaspeos*[7]	s	Cement Creek		1990	9, 10
23	3.9	96.1	100.0	100.0	*Circium arvense*	*Puccinia punctiformis*[7]	s	Roadside	= site a	1979	7
24	3.5	100.0	0	100.0	*Pulsatilla pratensis*	*Puccinia pulsatillae*[7]	s	Gårdby	perm. plot	1987	11
25	1.9	96.1	81.0	99.2	*Circium arvense*	*Puccinia punctiformis*[7]	s	Pasture	= site b	1979	7
26	1.6[9]	96.1[5]	90.0	99.6	*Circium arvense*	*Puccinia punctiformis*[7]	s	Netherlands	avg. of 4 nearby pops.	1989	6, 7

[1] The decrease in fitness of infected plants relative to uninfected plants was calculated as follows: 1 − (reproduction of infecteds × survival of infecteds)/(reproduction of uninfecteds × survival of uninfecteds).
[2] The decrease in fitness was not reported quantitatively, but was said to be low or none.
[3] The survival of systemically infected above ground shoots was zero, but the rhizomes survive, and only 4% of the population was systemically infected. Thus, the flowering decrease in a year was 4%.
[4] The decrease in fitness was estimated from a study in the same year at a nearby site (Cement Creek).
[5] Values used to derive the decrease in reproduction came from reference 7, the other data is from reference 6.
[6] *Puccinia seymouriana* and *Puccinia sparganioides* were not censused separately; fitness effects were determined in a common-garden experiment in which fungicides were used to keep the controls disease-free.
[7] The rust fungus is autoecious (lives on only one host species).
[8] The rust fungus is heteroecious (requires two unrelated host species).
[9] Weighted average of four plots (weighted by number of stems).

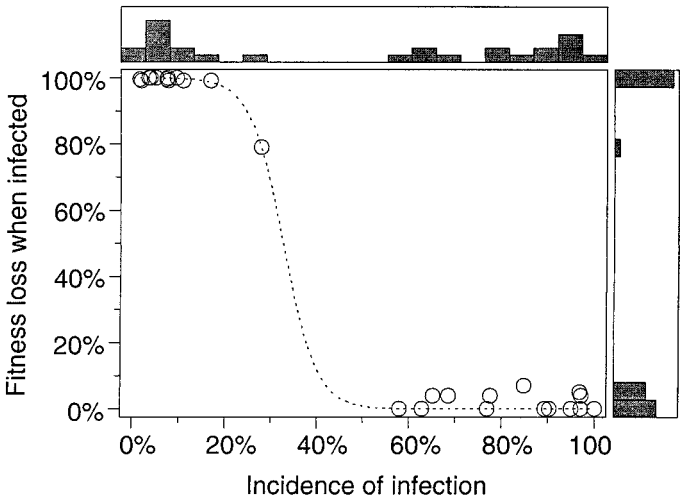


FIG. 4. Incidence of infection and fitness consequences of infection, in 26 plant populations infected by rust fungi (see Table 2). If variation in the incidence of infection reflects differences in disease resistance, and variation in fitness consequences reflects differences in tolerance, their distributions (shown by histograms) can be interpreted as indicating that resistance traits tend to be polymorphic, whereas tolerance traits tend to be fixed.

in the same host; strains that reproduce faster ''win'' the competition, but also do more damage to the host (Bull 1994; Frank 1996). Multiple infections are common in plant-pathogen systems (Jarosz and Davelos 1995) and are known to frequently occur in some of the cases listed in Table 2 (1, 3–8), thus making pathogen avirulence a less likely explanation than host tolerance. Nonetheless, deciding between pathogen avirulence and host tolerance requires controlled experiments. The evidence for host tolerance would be clear, if the fitness consequences of infection varied significantly among different host phenotypes. However, such variability should be rare, if tolerance traits move rapidly to fixation, as our analysis predicts.

Conversely, the evidence for pathogen benignness would be clear if the fitness consequences of infection varied among pathogen strains, but not among host strains. To our knowledge, experiments of this kind have not been performed in plant-pathogen systems. Until they are, it will not be possible to distinguish between universal host tolerance and universal pathogen benignness. Nonetheless, widespread host tolerance is consistent with the high disease incidence and low fitness consequences seen in many of the populations in Table 2.

In the populations in Table 2, the fitness consequences of infection are generally either very high or very low, with few intermediate values (Fig. 4). This stands in marked contrast to the more continuous distribution of disease incidence, which reflects variation in host resistance and environmental factors (Fig. 4). This pattern is again consistent with our theoretical analysis (Fig. 3), which predicts more polymorphism in resistance traits (and thus more populations that combine resistant and nonresistant individuals and therefore have intermediate levels of disease incidence). By contrast, tolerance traits should either be unable to invade (leaving the population uniformly nontolerant of infection) or be driven to fixation (leaving the population uniformly tolerant).

The incidence and fitness consequences of disease are negatively correlated (Fig. 4), suggesting that, as predicted, resistance and tolerance can be mutually redundant strategies. The populations in Table 2 exhibit high tolerance or high resistance, but not both (Fig. 4). There is a strong negative correlation between disease incidence and the fitness consequences of infection (Pearson's $r = -0.96$, Spearman's $r_s = -0.81$). This correlation could arise either through genetic or physiological trade-offs between resistance and tolerance traits or through the mutual redundancy of resistance and tolerance.

Negative correlations between disease incidence and its fitness consequences may also arise as a sampling artifact. Host populations subject to infection by widespread and highly lethal pathogens may not persist long enough to be noticed. Likewise, diseases may also go undetected if both their incidence and their consequences are small. However, the histograms in Figure 4 are much more difficult to explain as a sampling artifact: whereas disease incidence varies along a nearly continuous spectrum (suggesting that resistance is characteristically polymorphic), the fitness consequences of infection are strongly partitioned into either end of the spectrum (they are either inconsequential or severe).

If a pathogen has several different paths of action, its host may exhibit different levels of resistance and tolerance to its different modes of attack. For example, some rust fungi are particularly harmful to the host when they cause systemic infection, but seem to cause little damage when they form localized leaf lesions (Jarosz and Davelos 1995). One such system is *Puccinia punctiformis* and its host, the thistle *Circium arvense*; the host appears to have high tolerance and low resistance to leaf lesions (cases 13 and 14 of Table 2) and high resistance and low tolerance to systemic infections (cases 21, 23, 25, and 26 of Table 2). These complementary patterns of resistance and tolerance again suggest that they are redundant strategies.

Because tolerance traits are less likely to be variable in host populations, they are also less likely to be noticed. Variable traits can be readily recognized and quantified, but fixed traits are easily overlooked because they are not amenable to either measurement or experimentation. This problem is particularly acute for traits that, like tolerance, can only be measured through comparisons between different strains. Comparisons between strains can quantify components of tolerance that vary among them, but cannot measure the impact of any tolerance traits that they share in common. For example, suppose that we measured the fitness loss under infection in three different strains and found that these losses were 10%, 15%, and 20% (compared to the fitness of uninfected individuals from the same strains). We would correctly conclude that some variable trait is responsible for the observed difference in tolerance between the three strains. However, if these three strains also share a common fixed trait (without which their fitness losses would instead be, say, 60%, 70%, and 80%, respectively), this fixed component will not be detectable precisely because it is not variable, even though it accounts for the majority of the tolerance in all three strains.

Although it is difficult to study traits that are fixed within a species, one can look for variation in such traits among

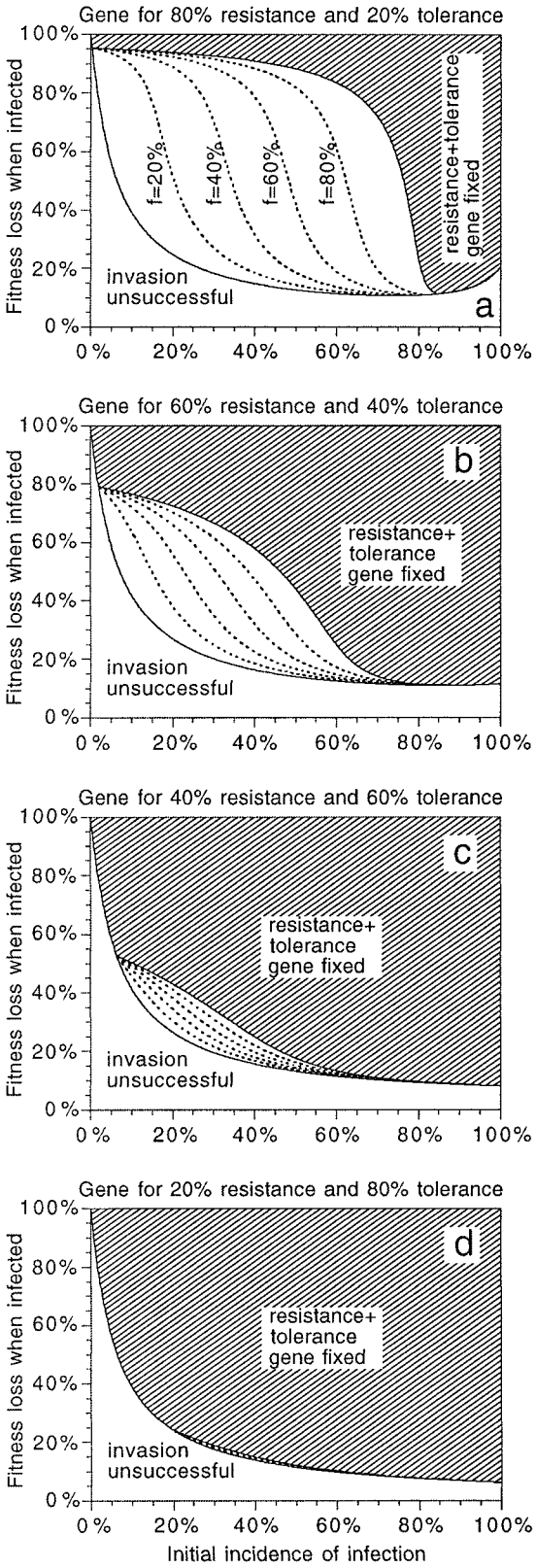


FIG. 5. Equilibrium phenotype frequencies for traits conferring both resistance and tolerance, in varying degrees. Plot axes and symbols are identical to those shown in Figure 3. Each panel shows the steady-state frequency for a single trait that combines resistance and tolerance characteristics. The four panels depict traits that can successfully invade under nearly equivalent ranges of conditions.

species. For example, vegetative reproduction may be an important tolerance mechanism in plants because it allows them to have many growth points; if one is attacked, the others can compensate (Clay and van der Putten 1999). Vegetative reproduction is generally universally present or universally absent within a species, as we would expect for an important tolerance trait that has arisen (and become fixed) in some species, but not others.

Despite our theoretical expectation that tolerance traits should be fixed, there are several reasons why real or apparent polymorphisms may exist in nature. First, if the incidence of infection (or herbivory) fluctuates through time, selection may not act consistently enough to fix tolerance traits. Second, if a tolerance trait is disadvantageous in some populations (because the incidence of attack is low), polymorphism will exist at the metapopulation level even if fixation (at $f_{RT} = 0$ or $f_{RT} = 1$) prevails in the individual populations. Studies that have reported variation in tolerance to herbivory (e.g., Mauricio et al. 1997; Stowe 1998; Strauss and Agrawal 1999) may reflect this phenomenon, or they may reflect polymorphism in tolerance traits themselves. Third, gene flow between populations with different selection regimes (some favoring a tolerance trait and others opposing it) will prevent fixation from occurring in the individual populations. Fourth, many traits that confer increased tolerance (such as traits promoting rapid growth) affect fitness in other ways as well; they will therefore be subject to many different selection pressures, including those that are unrelated to disease or herbivory. These conflicting selection pressures are likely to inhibit fixation of such traits. Finally, if resistance and tolerance are genetically linked, frequency-dependent selection on resistance will inhibit fixation of both resistance and tolerance (see below).

Evolution of Combined Resistance/Tolerance Traits

Individual traits can combine resistance and tolerance characteristics; polymorphism should be more common in traits with stronger resistance components, and fixation should be more common in traits with stronger tolerance components. Resistance and tolerance traits can be genetically linked (Stowe 1998), or they can be pleiotropic, with a single host trait altering both the incidence of disease and a host's tolerance of it. One such trait that combines tolerance and resistance is slow rusting in cereal crops. Slow rusting delays fungal reproduction, thus reducing the risk of autoinfection and the rate of transmission to new hosts (Vanderplank 1984). Slow rusting also acts as a tolerance trait because it delays damage until later in the growing season, often allowing the host to reproduce before infection becomes severe. Because individual traits can combine resistance and tolerance characteristics, we simulated the evolutionary fate of several such

←

However, traits that confer higher levels of tolerance and lower levels of resistance are markedly more likely to become fixed and markedly less likely to be polymorphic. Levels of resistance and tolerance, which are specified above each panel, are R and T in equations (6) and (7), respectively; all traits carry a fitness cost (C) of 5%.

traits with different amounts of tolerance and resistance (Fig. 5). Each of these traits is favored by selection (and thus can invade) under similar conditions of pathogen infectiousness and virulence. However, traits with stronger resistance components will tend to be polymorphic—and traits with stronger tolerance components will tend to become fixed—over wider ranges of conditions. Interestingly, slow rusting is stable and durable over time (Vanderplank 1984) as our analysis would predict for a trait that is dominated by tolerance. Mixed resistance/tolerance traits that are, like slow rusting, controlled by one or a few genes (Vanderplank 1984), should conform to the pattern of behavior shown in Figure 5. However, traits as complex as resistance and tolerance will often be controlled by many genes. Accordingly, we have extended the analysis developed here using a quantitative genetics approach (J. W. Kirchner and B. A. Roy, unpubl. data); that approach yields patterns of behavior that are consistent with the results reported here.

Coevolutionary Origins of Mutualism via Host Tolerance

The coevolution of hosts and pathogens should reinforce polymorphism in resistance traits and fixation in tolerance traits. Because resistance traits directly threaten pathogen fitness, they create evolutionary incentives for pathogens to evade them, leading to continually shifting patterns of host resistance and pathogen infectiousness. Host resistance defenses create a coevolutionary ''arm's race'' that hosts are unlikely to win; pathogens have repeatedly demonstrated that they can rapidly evolve to evade antibiotics, pesticides, and host defenses (Schafer 1971; Clarke 1986; Brown 1996; Baquero and Blázquez 1997). By contrast, host tolerance strategies avoid such arms races because they do not diminish infection and thus do not threaten pathogen survival. As a result, they may be coevolutionarily stable. In this coevolutionary context, breeding for increased tolerance may be a promising pest management strategy (Schafer 1971; Clarke 1986).

Our results suggest that mutualism may evolve from parasitism through natural selection for host tolerance, rather than pathogen avirulence, as others (Boucher et al. 1982; Thompson 1994) *have suggested.* Host tolerance strategies can form the basis for stable host-pathogen associations that give neither host nor pathogen an evolutionary incentive to defect. Pathogen avirulence is selected against whenever pathogen strains compete within a host (Bull 1994; Frank 1996). No such competitive mechanisms act against host tolerance strategies, and pathogens have no evolutionary incentive to evade them—in marked contrast to host resistance defenses, which create strong selection for pathogens that outwit them (Schafer 1971; Clarke 1986). The genetics of tolerance-based associations are also likely to be stable because tolerance genes will tend to be fixed in the host population. Because host tolerance genes are not moving targets, pathogens can more readily evolve close associations with them. These evolutionary forces encourage stable associations between pathogens and hosts, which are a prerequisite for mutualism.

Acknowledgments

We thank H. M. Alexander, P. Schmid-Hempel, N. Paul, M. Turelli, the anonymous reviewers, and L. Nunney for their comments on earlier versions of the manuscript. This work was supported by Swiss National Fund grant 3100–046865.96 to BAR and National Science Foundation grant EAR-9357931 to JWK.

Literature Cited

Alexander, H. M. 1991. Plant population heterogeneity and pathogen and herbivore levels: a field experiment. Oecologia 86: 125–131.

Anderson, R. M., and R. M. May. 1991. Infectious diseases of humans: dynamics and control. Oxford Univ. Press, Oxford, U.K.

Baquero, F., and J. Blázquez. 1997. Evolution of antibiotic resistance. Trends Ecol. Evol. 12:482–487.

Bergelson, J., and C. B. Purrington. 1996. Surveying patterns in the cost of resistance in plants. Am. Nat. 148:536–558.

Boucher, D. H., S. James, and K. H. Keeler. 1982. The ecology of mutualism. Annu. Rev. Ecol. Syst. 13:315–347.

Brown, T. M. 1996. Molecular genetics and evolution of pesticide resistance. American Chemical Society, Washington, DC.

Bull, J. J. 1994. Virulence. Evolution 48:1423–1437.

Clarke, D. D. 1986. Tolerance of parasites and disease in plants and its significance in host-parasite interactions. Adv. Plant Pathol. 5:161–197.

Clay, K., and P. X. Kover. 1996. The red queen hypothesis and plant/pathogen interactions. Annu. Rev. Phytopathol. 34:29–50.

Clay, K., and W. van der Putten. 1999. Pathogens and plant life histories. Pp. 275–302 *in* T. Vuorisalo and P. Mutikainen, eds. Life history evolution in plants. Kluwer Academic Publishers, Dordrecht, The Netherlands.

Davelos, A. L., H. M. Alexander, and N. A. Slade. 1996. Ecological genetic interactions between a clonal host plant (*Spartina pectinata*) and associated rust fungi (*Puccinia seymouriana* and *Puccinia sparganioides*). Oecologia 105:205–213.

Dobson, A. P., and E. R. Carper. 1996. Infectious diseases and human population history. Bioscience 46:115–125.

Dobson, A., and M. Crawley. 1994. Pathogens and the structure of plant communities. Trends Ecol. Evol. 9:393–398.

Fineblum, W. L., and M. D. Rausher. 1995. Tradeoff between resistance and tolerance to herbivore damage in a morning glory. Nature 377:517–520.

Frank, S. A. 1996. Models of parasite virulence. Quart. Rev. Biol. 71:37–78.

Frantzen, J. 1994. An epidemiological study of *Puccinia punctiformis* (Str.) Röhl as a stepping-stone to the biological control of *Cirsium arvense* (L.) Scop. New Phytol. 127:147–154.

Gillespie, J. H. 1975. Natural selection for resistance to epidemics. Ecology 56:493–495.

Herms, D. A., and W. J. Mattson. 1992. The dilemma of plants: to grow or to defend. Quart. Rev. Biol. 67:283–335.

Hiers, J. K., and J. P. Evans. 1997. Effects of anthracnose on dogwood mortality and forest composition of the Cumberland Plateau (USA). Conserv. Biol. 11:1430–1435.

Jarosz, A. M., and A. L. Davelos. 1995. Effects of disease in wild populations and the evolution of pathogen aggressiveness. New Phytol. 129:371–387.

Klinkowski, M. 1970. Catastrophic plant diseases. Annu. Rev. Phytopathol. 8:37–60.

Lenski, R. E., and R. M. May. 1994. The evolution of virulence in parasites and pathogens: reconciliation between two competing hypotheses. J. Theor. Biol. 169:253–265.

Leonard, K. J., and R. J. Czochor. 1980. Theory of genetic interactions among populations of plants and their pathogens. Annu. Rev. Phytopathol. 18:237–258.

Lively, C. M. 1996. Host-parasite coevolution and sex. Bioscience 46:107–114.

Marquis, R. J. 1992. Selective impact of herbivores. Pp. 301–325

in R. S. Fritz and E. L. Simms, eds. Plant resistance to herbivores and pathogens. Univ. of Chicago Press, Chicago, IL.
Mauricio, R., M. D. Rausher, and D. S. Burdick. 1997. Variation in the defense strategies of plants: are resistance and tolerance mutually exclusive? Ecology 78:1301–1311.
May, R. M., and R. M. Anderson. 1983. Epidemiology and genetics in the coevolution of parasites and hosts. Proc. R. Soc. Lond. B 219:281–313.
Paige, K. N., and T. Whitham. 1987. Overcompensation in response to mammalian herbivory: the advantage of being eaten. Am. Nat. 129:407–416.
Parker, M. A. 1987. Pathogen impact on sexual vs. asexual reproductive success in *Arisaema triphyllum.* Am. J. Bot. 74: 1758–1763.
Price, P. W., M. Westoby, B. Rice, P. R. Atsatt, R. S. Fritz, J. N. Thompson, and K. Mobley. 1986. Parasite mediation in ecological interactions. Annu. Rev. Ecol. Syst. 17:487–505.
Rosenthal, J. P., and S. C. Welter. 1995. Tolerance to herbivory by a stemboring caterpillar in architecturally distinct maizes and wild relative. Oecologia 102:146–155.
Roy, B. A. 1993. Patterns of rust infection as a function of host genetic diversity and host density in natural populations of the apomictic crucifer, *Arabis holboellii.* Evolution 47:111–124.
Roy, B. A., and P. Bierzychudek. 1993. The potential for rust infection to cause natural selection in apomictic *Arabis holboellii* (Brassicaceae). Oecologia 95:533–541.
Roy, B. A., J. W. Kirchner, C. Christian, and L. Rose. 1997. High disease incidence and disease tolerance in a Great Basin community. Bull. Ecol. Soc. Am. (Suppl.) 78:173.
Schafer, J. F. 1971. Tolerance to plant disease. Annu. Rev. Phytopathol. 9:235–252.
Simms, E. L., and M. D. Rausher. 1987. Costs and benefits of plant resistance to herbivory. Am. Nat. 130:570–581.
Simms, E. L., and J. Triplett. 1994. Costs and benefits of plant responses to disease: resistance and tolerance. Evolution 48: 1933–1945.
Stowe, K. A. 1998. Experimental evolution of resistance in *Brassica rapa*: correlated response of tolerance in lines selected for glucosinolate content. Evolution 52:703–712.
Strauss, S. Y., and A. A. Agrawal. 1999. The ecology and evolution of plant tolerance to herbivory. Trends Ecol. Evol. 14:179–185.
Thompson, J. N. 1994. The coevolutionary process. Univ. of Chicago Press, Chicago. IL.
Tiffin, P. 2000. Are tolerance, avoidance, and antibiosis evolutionarily and ecologically equivalent responses of plants to herbivores? Am. Nat. *In press.*
Van der Meijden, E., M. Wijn, and H. J. Verkaar. 1988. Defense and regrowth, alternative plant strategies in the struggle against herbivores. Oikos 51:355–363.
Vanderplank, J. E. 1984. Disease resistance in plants. Academic Press, Orlando.
Watson, A. K., and W. J. Keogh. 1981. Mortality of Canada thistle due to *Puccinia punctiformis.* Pp. 325–332 *in* Proceedings of the 5th International Symposium Biology Contr. Weeds. Brisbane, Australia.
Wennström, A., and L. Ericson. 1991. Variation in disease incidence in grazed and ungrazed sites for the system *Pulsatilla pratensis.* Oikos 60:35–39.
Wennström, A., L. Ericson, and J. Elveland. 1995. The dynamics of the plant *Lactuca sibirica* and the frequency of its rust *Puccinia minussensis* in river valleys in northern Sweden. Oikos 72: 288–292.

Corresponding Editor: L. Nunney

Appendix

Parameter Estimation

To find the equilibrium frequency of the resistance/tolerance trait, we must stipulate its three characteristics: the level of resistance (R), the level of tolerance (T), and the fitness cost of expressing the trait (C). We also must stipulate three characteristics of the host-pathogen system: the fitness loss under infection (L_o), the pathogen transmission coefficient (β_o), and the uninfected host lifespan (τ). At equilibrium, the reproduction rate, a_o, need not be specified because when equations (9) and (10) are set equal to one another, a factor of $a_o\tau$ cancels from each. After that factor is canceled, β_o and τ do not need to be specified separately because they appear together as their product, $\beta_o\tau$. Even so, it would be helpful if $\beta_o\tau$ could be expressed directly in terms of readily observable quantities. It turns out that this can be done, if one knows what the equilibrium incidence of infection would be in a population composed entirely of the reference strain (e.g., before an invasion experiment in which the resistant/tolerant trait is introduced). For the initial (i.e., preinvasion) level of infection, I_{init}, in the reference strain, we can rewrite equation (2) as:

$$\beta_o\tau = \frac{1}{(1 - I_{init})}\frac{1}{(1 - L_o)}. \tag{A1}$$

Thus, the equilibrium is completely specified by two characteristics of the pathogen (its infectiousness, I_{init}, and its virulence, L_o in the reference strain) and three characteristics of the resistance-tolerance trait (R, T, and C).

We have defined these five characteristics so that they can potentially be measured in real host-pathogen systems. The pathogen infectiousness (I_{init}) could be measured by the incidence of infection in a population of the reference strain. The pathogen's virulence (L_o) could be measured by comparing the fitness of infected and uninfected individuals from the reference strain. The level of tolerance (T) could be measured by comparing the fitness loss under infection in the resistant/tolerant strain versus the reference strain. The level of resistance (R) could be measured by comparing the incidence of infection in the resistant/tolerant and reference host strains; combining equations (2) and (6), one can show that:

$$R = 1 - \left(\frac{I_{RT}}{1 - I_{RT}}\right)\left(\frac{1 - I_o}{I_o}\right)\left(\frac{1 - L_o}{1 - L_{RT}}\right). \tag{A2}$$

Finally, the fitness cost (C) of resistance/tolerance could be measured by comparing the fitness of uninfected hosts in the resistant/tolerant and reference strains.