The Evolutionary Genetics of Plant-Pathogen Systems

Understanding the coevolution of hosts and parasites is key to understanding their ecology

Ellen L. Simms

There was a mountain just across the valley.... It wasn't very tall and it was covered up completely with chestnut trees.... And that's where we'd usually go to get our crop of chestnuts. But they all died in one summer. Every one of 'em. They just quit having nuts. There weren't any more. And there [used to be] thousands of bushels of 'em shipped out of these mountains to cities. They was sold in the fruit stands and sidewalk stores in all the big cities because everybody liked them, you know. They were cheap.
—(Noel Moore, quoted in Rice et al. 1980)

In a host-parasite system the level of genetic variance in resistance and virulence can strongly influence the population dynamics and equilibrium of the interacting species

The chestnut blight was first noticed in the New York Zoological Gardens in 1904 (Rice et al. 1980); within 50 years the disease had swept across the eastern deciduous forests, leaving 3.6 million hectares of American chestnut trees (*Castanea dentata*) dead or dying (Anagnostakis 1987). Once an economically, socially, and ecologically important component of the hardwood forests of the eastern United States (Anagnostakis 1987), American chestnuts persist today only as dwindling stump sprouts from rootstocks of these once magnificent trees (Griffin 1992). The loss of mature chestnut trees to the blight fungus, *Cryphonectria parasitica*, has reduced the carrying capacity of Appalachian forests for wild animals (Griffin 1992) and deprived humans and domesticated animals of an important source of food and income (Rice et al. 1980). As the chestnut blight pandemic illustrates, infectious diseases can dramatically alter biological communities. However, coevolution between hosts and pathogens is likely to condition the states of traits, such as resistance and virulence, that are important to the host-pathogen interaction. Understanding how pathogens and their hosts coevolve is therefore critical to understanding how this interaction is likely to influence communities. In this article I briefly describe how pathogens may affect biological communities and then examine in more depth our understanding of the evolution of plants and their microbial pathogens.

Population ranges and community diversity. The outcome of competition between pairs of species may depend upon the presence or absence of disease-inducing parasites[1] (Park 1948). In Maine and Nova Scotia, white-tailed deer (*Odocoileus virginianus*) have replaced moose (*Alces alces*) as the dominant cervid because deer are tolerant carriers of the meningeal worm, *Parelaphostrongylus tenuis*, which causes severe neurological damage to other cervids (Anderson 1972). After mosquitoes were introduced to Hawaii in 1826, avian malaria played an important role in the extinction of many Hawaiian land birds (Warner 1968) and significantly restricted the distributions of others (van Riper et al. 1986).

Parasites may also hinder repopulation of ancestral ranges or migration into new areas (Price 1980). The meningeal worm may be blocking reintroduction of woodland caribou (*Rangifer trandus caribou*) into habitats now occupied by white-tailed deer (Anderson and Prestwood 1979). In another example, the RNA virus that causes rinderpest eliminated certain artiodactyls from such large areas of Africa (May 1983) that lack of hosts led to the extermination of tsetse flies (*Glossina*) and the sleeping sickness–causing try-

Ellen L. Simms is an assistant professor in the Department of Ecology and Evolution at the University of Chicago, Chicago, IL 60637. She studies the evolution of plant interactions with other organisms, including herbivores, pathogens, and mutualists.

[1]The terms *parasite* and *pathogen* are used interchangeably in this article.

panosome they carry (Stevenson-Hamilton 1957). With sleeping sickness eliminated, humans and domesticated animals invaded these regions, rendering them unavailable to repopulation by the original native artiodactyls (Stiling 1992).

Finally, disease-causing parasites may assume a keystone role, increasing species diversity by undermining the competitive superiority of their host and permitting persistence of an inferior competitor (Burdon and Chilvers 1977). This keystone function may even be important in ecological succession. For example, a soil-borne pathogen causes degradation of beach grass, *Ammophila arenaria*, thereby facilitating replacement of early successional species by later species on coastal foredunes in northern Europe (Van der Putten and Troestra 1990, Van der Putten et al. 1993).

Population dynamics and classical biological control. Success stories in the biological control literature offer ample evidence of the ability of parasites to control host population densities (DeBach 1974). A classic example is the use of myxoma virus to control European rabbits (*Oryctolagus cuniculus*) in Australia. This example is particularly valuable because, unlike many biocontrol efforts, it was closely monitored over the decades subsequent to the release of the pathogen (Fenner and Myers 1978, Fenner and Radcliffe 1965, Fenner et al. 1956, 1957). Initially, infections were fatal more than 99% of the time, but within a year after release this value had dropped to 90%. Mortality continued to decline in subsequent years (Fenner and Woodroofe 1965) because of the evolution of both increased resistance in the rabbit population and decreased viral virulence. Although the virus was still the major controlling agent of rabbits in Australia in the mid-1980s (Parer et al. 1985), it remains unclear whether this situation is likely to persist. The system might reach an evolutionary equilibrium at which the disease can still control the host population. Alternatively, directional evolutionary change could result in extinction of the rabbit if disease virulence outruns host resistance. Then again, if host resistance evolves more quickly than viral virulence, the disease may cease to control the rabbit. Detailed modeling by Dwyer and colleagues (1990) suggests that the virus is likely to remain an effective control agent in the near future. However, predicting the longer term outcome of this coevolutionary interaction between rabbit and virus is likely to require greater knowledge of the genetic structure of the two populations.

In a host-parasite system the level of genetic variance in resistance and virulence can strongly influence the population dynamics and equilibrium of the interacting species (Frank 1993, Seger 1992). Ecologically unstable systems can be stabilized by the presence of sufficient genetic variance in virulence and resistance (Saloniemi 1993). Thus, predicting the population dynamics and possible equilibrium states of a host-parasite system depends on knowing whether genetic diversity for resistance and virulence is likely to persist in the system.

Table 1. Phenotypic outcome of interaction between host and pathogen predicted by the gene-for-gene complementation system. When the avirulent (*V*) pathogen matches the appropriate host resistance allele (*R*), a hypersensitive response by the host is likely to prevent infection (-). In all other cases (susceptible host [*rr*], virulent pathogen [*v*], or both), a compatible reaction is likely to result in successful infection (+).

Pathogen genotype	Host genotype		
	RR	*Rr*	*rr*
VV	-	-	+
Vv	-	-	+
vv	+	+	+

Genetic models of host-parasite coevolution

The mutually antagonistic interaction between host and parasite is often called an arms race (van Valen 1973). Several models have been developed to examine how negative effects of disease on host fitness select for the evolution of resistance and how negative effects of resistance on parasite fitness select for the evolution of virulence (Burdon 1987, Seger 1992, Thompson 1994). In this article I describe the assumptions and predictions of these models.

The earliest models of host-parasite coevolution (e.g., Leonard 1977, Mode 1958, 1961) were inspired by Flor's (1956) discovery that individual dominant resistance alleles in flax (*Linum usatitissimum*) are complemented by specific recessive virulence alleles in the fungal parasite that causes flax rust (*Melampsora lini*; Table 1). These relatively simple models all assume that resistance and virulence are beneficial to the organisms possessing each trait. Most models also assume that these traits involve fitness costs, or trade-offs. A trade-off is defined as the fitness decrement experienced by an individual possessing a trait, either virulence or resistance, as measured in an environment where it is not needed (Simms 1992). Costs of virulence are incorporated in these models as reduced fitness of the virulent pathogen relative to that of the avirulent strain when each infects a susceptible host. Resistance costs are depicted as reduced fitness of the resistant host relative to that of the susceptible host in a disease-free environment (Table 2). When costs are absent, these models predict that

Table 2. Host and pathogen fitnesses in the model developed by Leonard (1977). k = cost of virulence; t = extent to which resistance depresses pathogen fitness; a = advantage to the pathogen of possessing a matching virulence gene; s = extent to which infection by the avirulent pathogen depresses fitness in the susceptible host; and c = cost of resistance.

Host genotype	Host fitnesses		Pathogen fitnesses	
	V (avirulent)	*v* (virulent)	*V* (avirulent)	*v* (virulent)
rr (susceptible)	$1 - s$	$1 - s(1 - k)$	1	$1 - k$
R*r*/RR (resistant)	$1 - c - s(1 - t)$	$1 - c - s(1 - k + a)$	$1 - t$	$1 - k + a$

the virulence allele will become fixed in the pathogen population, rendering the resistance allele selectively neutral. Because neutral alleles may be lost or fixed by genetic drift (Kimura 1983), genetic variance is not likely to be maintained. Selection is likely to then favor any new host allele that confers resistance to the new virulence allele in the pathogen. Because new resistance alleles are constantly needed by the host to avoid infection and new virulence alleles are required by the pathogen to overcome these defenses, van Valen (1973) named this process for the Red Queen encountered by Alice in Wonderland. The Red Queen complained that in Wonderland, one must always be running just to stay in place.

When virulence and resistance are both costly, these simple genetic models predict cycling of host and pathogen allele frequencies around a locally unstable equilibrium point (Burdon 1987, Seger 1992). Cycling occurs because negative frequency-dependent selection on resistance and virulence is indirect and time-delayed (Seger 1992). Alleles common in the current generation are less fit in a future generation; hence the time delay. Frequency dependence is indirect because the fitness of each host genotype depends on the frequency of virulence alleles in the pathogen population, and the fitness of each pathogen genotype depends on the frequency of resistance alleles in the host population. For example, a newly mutated resistance allele confers high fitness because virulence to that allele is initially rare (or absent) in the pathogen population. Initially, the new host gene is also rare and has little selective influence on the pathogen population. However, as the novel resistance trait spreads in the host population, any pathogens possessing virulence to that gene are likely to obtain a fitness advantage via access to an unused resource. Pathogen virulence is likely to then spread, reducing the fitness advantage of the once-novel resistance allele.

Even a slight increase in the complexity of the transmission genetics underlying resistance and virulence causes the behavior of these models to become extraordinarily complex. For example, treating the host as diploid with several alleles at a single resistance locus and incorporating multiple alleles at a haploid pathogen virulence locus are likely to produce patterns resembling chaos (Seger 1992). On the other hand, quantitative inheritance may reduce the complexity of evolutionary dynamics. When resistance is modeled independent of virulence and treated as a continuously variable trait determined by small contributions of many alleles at a large number of loci, the trade-off between costs and benefits can produce stabilizing selection for an intermediate optimal value of resistance (Simms 1992, Simms and Rausher 1987). In the absence of any other evolutionary force, stabilizing selection on a quantitative trait is likely to erode genetic variance at the loci affecting the trait (Scharloo 1964, Wright 1969). Seger (1992) provides a lucidly intuitive description of why this is so.

Frank (1995) published a quantitative genetic model that considers coevolution of both host and pathogen simultaneously. This model corroborates the conclusions of previous evolutionary models of resistance: In the presence of a sufficiently large pathogen population, stabilizing selection can produce an intermediate level of resistance with little genetic variance. However, the evolutionary outcome depends on the shape of the benefit function. Earlier models assumed that the benefit of resistance increases at a decelerating rate with increasing allocation to resistance (Fagerström et al. 1987, Simms and Rausher 1987). If benefits instead increase at an accelerating rate, selection on resistance is likely to be disruptive, producing a bimodal distribution of host phenotypes. In this case, under certain ecological circumstances, genetic variance can be maintained in the host population (Frank 1993).

In the quantitative genetic model, evolution of virulence in the pathogen is influenced by the interaction of two factors. As in hosts, decelerating benefits of virulence are likely to produce stabilizing selection and little genetic variance, whereas accelerating benefits are likely to produce disruptive selection and potentially large amounts of genetic variance. However, the distribution of host genotypes also influences equilibrium genetic variance in virulence. A bimodal distribution of resistance phenotypes, due to disruptive selection on the host population, is likely to produce bimodality in pathogen phenotypes. As was true for resistance, a bimodal distribution of virulence phenotypes may maintain substantial levels of genetic variance in the pathogen population (Frank 1993).

Three major messages arise from antagonistic models of host-pathogen coevolution. First, the specific modes of genetic transmission of resistance and virulence are important factors determining the evolutionary behaviors and equilibria of host-parasite systems. A second determining factor is the array of trade-offs, or costs, associated with resistance in the host and virulence in the parasite. Some trade-offs can arise from the costs of maintaining relevant biochemical pathways or allocating resources to resistance or virulence (Simms 1992). Furthermore, if resistance and virulence traits are specifically targeted in a one-to-one complementary fashion, another trade-off can occur when, for example, virulence to one form of resistance makes a pathogen relatively less fit on hosts lacking that resistance trait (Parker 1992). Thus the specificity of resistance and virulence is a third important factor that influences evolutionary outcome in a host-pathogen system.

To understand how pathogens influence host ecology, we must assess the validity of the assumption that virulence and resistance involve fitness trade-offs as well as determine the nature of genetic transmission of these traits in particular host-pathogen systems. The first and arguably some of the best understood systems of genetically controlled disease compatibility are found in plants. Consequently, this article focuses on the genetics of resistance and virulence in phytopathogenic systems.

Biology of phytopathogenic organisms

Although infectious diseases of plants may be caused by many kinds

of microorganisms, this article considers mainly fungal and bacterial infections. Fungi that cause plant diseases can be classified into three ecological categories: necrotrophs, biotrophs, and hemibiotrophs.

Necrotrophs invade living tissue but then kill it for nourishment. They often cause cell death by means of host-specific toxins, and plant resistance against them can involve detoxification mechanisms or modification of toxin target sites. Necrotrophs tend to have a wide host range and can also grow in axenic culture.

In contrast, biotrophs obtain nutrition from living plant tissue. Plant resistance to biotrophs frequently involves a hypersensitive response. Because of their intimate dependence upon their hosts, biotrophs generally have highly specific host ranges. They also tend to be obligate parasites and can only rarely be cultured on synthetic medium.

Hemibiotrophic fungi have both biotrophic and necrotrophic components in their life histories. In these fungi, including species of *Colletotrichum (Glomerella)*, *Fulvi (Cladosporium)*, *Magnaporthe (Pyricularia)*, and *Phytophthora*, the biotrophic phase is restricted to the initial infected cell (Tyler 1993). Hemibiotrophs grow readily in culture but vary in host range.

In contrast to phytopathogenic fungi, which are appallingly diverse, bacterial plant pathogens are limited to only a few genera (Bailey 1991). Three genera, *Erwinia*, *Pseudomonas*, and *Xanthomonas*, have been studied in most detail. They are easily grown in culture, and many sophisticated molecular and genetic tools are available to study virulence in these phytopathogens.

The infection process and terminology

Successful infection of a host is a complex multistep process. The pathogen must find and recognize its host, invade host tissues, withstand any defenses, and proliferate within the host. Finally, progeny or propagules must be disseminated to an environment in which new hosts can be encountered.

For microbial disease agents, finding the host is generally a nonspecific process. Most microbes have little control over their movements, being instead dependent on air or water currents, or on the movements of hosts and/or vectors. Host resistance at this stage generally takes the form of *disease avoidance* (Thrall et al. 1993); for example, a host may be dormant when the parasite is present (Burdon 1987).

After a potential host has been located, its suitability for infection becomes an issue. Most organisms are resistant to most pathogens; only particular combinations of host genotype, microbe genotype, and environment produce a compatible interaction leading to disease. Some pathogens may require specific surface characteristics, such as hardness or hydrophobicity, or topographic features, such as ridges or grooves, as germination stimulants or to direct growth of germ tubes (Gow 1993, Kolattukudy et al. 1995). The pathogen must also penetrate mechanical barriers to infection. Such characteristics are important features of plant resistance but are generally not involved in determining specific resistance or susceptibility of cultivars or species (Bailey 1991). Furthermore, much of the research on the molecular genetic basis of plant resistance bypasses host barriers by vacuum infiltrating microbes directly into host tissue.

Once it enters host tissue, the pathogen must run a gauntlet of both induced and constitutive defenses. It is at this point that the specificity of plant-pathogen interactions is determined. The pathogen must possess metabolic pathways that allow it to live in and feed on host tissue (termed *pathogenicity*) as well as to avoid ringing the alarm bells of the plant. These alarms often summon the host's rapidly induced defenses to the infection site.

One reaction, termed the *hypersensitive response*, frequently involves death of cells in and around the infected area, production and accumulation of hydrogen peroxide during an oxidative burst (Tenhaken et al. 1995), and the subsequent accumulation of phenolics, phytoalexins, chitinases, and other pathogenesis-related proteins in cells surrounding the infected tissue (Bailey and O'Connell 1989). The hypersensitive response is triggered when the plant recognizes particular compounds produced by the invading pathogen. Pathogen genotypes that produce these compounds are termed *avirulent* or *incompatible*, because their invasion of the plant is checked by the hypersensitive response they elicit. Pathogen genotypes that do not produce these compounds are termed *virulent* or *compatible*, because they can evade detection by the plant. To successfully infect a resistant plant, a microbe must be both virulent and pathogenic.

The invading pathogen may also induce a systemic response that decreases the probability of subsequent infection of existing tissues elsewhere in the host (Ryals et al. 1991, 1995). Large-scale tissue loss may even stimulate a developmental response involving the production of new tissue that is more resistant to damage than older tissue (Bryant et al. 1988).

Genetics of resistance and virulence

As described previously, mathematical models of host-pathogen interactions indicate that the ecological and evolutionary outcomes of these interactions depend in part on the mode of inheritance of resistance and virulence. Although there is a great variety of mechanisms by which these traits are inherited, much of the current research centers on resistance and virulence involved in gene-for-gene systems of host-pathogen interaction.

Gene-for-gene interactions. The dominant genetic paradigm of plant-pathogen interaction derives from Flor's (1956) pioneering work describing the complementary gene-for-gene system of flax and its obligately biotrophic fungal pathogen, flax rust. This type of interaction has since been described for a number of phytopathogenic systems (Day 1974, Thompson 1994, Thompson and Burdon 1992). Usually, plant resistance genes are dominant and pathogen virulence genes are recessive. When the host possesses the

dominant resistance allele (*R*), infection by the avirulent (*V*) pathogen provokes a hypersensitive response in the plant. All other combinations of alleles at the resistance and virulence loci are compatible and result in successful infection (Table 1).

The molecular model proposed to explain this pattern invokes the action of chemical signaling between plant and pathogen (de Wit 1992, Keen 1990). The model posits that an incompatible reaction occurs because resistant plants can recognize and respond to a gene product of the avirulent pathogen genotype. Pathogens evade host detection and acquire virulence (*v*) by ceasing to produce the recognizable gene product.

Although gene-for-gene interactions between plants and biotrophic fungi provided the first and most widely recognized paradigm of specific host-pathogen resistance, the obligate biotrophy of these fungi has hampered detailed molecular genetic work on them. However, other types of phytopathogenic organisms, ranging from hemibiotrophic fungi to bacteria and viruses, can also induce a hypersensitive response (Keen 1993) and often conform to the gene-for-gene model. Consequently, most research on the genetics of virulence and resistance involving the hypersensitive response has focused on these more tractable organisms.

This research has revealed that induction of the hypersensitive host response is conditioned by avirulence (*avr*) and hypersensitive reaction and pathogenicity (*hrp*) genes in the pathogen (Gabriel 1986). Avirulence genes produce a pattern of dominant resistance and recessive virulence reminiscent of that found by Flor (1955) in flax and flax rust. As predicted, *avr* genes encode products that are positive factors in the generation of a resistance response in the host (Lindsay et al. 1993). These products are called elicitors (Keen 1975) because they interact directly with the plant to elicit the host hypersensitive response. A pathogen that is "wild type" at an *avr* gene produces the elicitor and is therefore avirulent (*V*), incapable of infecting a resistant host. A mutation in an *avr* gene deactivates its elicitor, which prevents the elicitor from inducing the host hypersensitive response. Thus *avr* mutants are virulent (*v*) and can infect a resistant host. Unlike *avr* genes, *hrp* genes are essential to growth inside a plant. The *hrp* mutants cannot cause disease, even on a susceptible host. Moreover, they generally do not elicit a hypersensitive response on nonhost species or resistant host genotypes (Long and Staskawicz 1993).

Plant resistance genes: receptors? It is presumed by Keen (1993) and others that some types of plant resistance involve genes encoding receptors for pathogen-produced elicitors, and a major goal of recent research has been to identify these postulated receptors. After decades of work, resistance genes complementary to known avirulence genes are being identified and sequenced (Ausubel et al. 1995, Dinesh-Kumar et al. 1995, Martin et al. 1993, Moffat 1994). Because the products of these genes have not yet been identified, their mode of function remains a matter of speculation. For example, the amino acid sequence of *RPS2*, which confers resistance to the bacterial pathogen *Pseudomonas syringae* in the mouse-eared cress, *Arabidopsis thaliana*, suggests that it may have a membrane-spanning domain (Bent et al. 1994). Such a protein could be exposed on the cell surface and might thus act as a receptor of extracellular signals.

However, resistance does not necessarily involve only receptors. For example, it may be that the ability to produce glucanase is in part responsible for the general resistance of soybeans (*Glycine max*) to *Phytophthora*. When glucanase activity is increased, soybeans become more resistant to infection (Yoshikawa et al. 1990), and expression of the cloned soybean glucanase gene in transgenic tobacco confers general resistance to several pathogens, including *Phytophthora*. Thus, glucanases, which are enzymes that degrade glucans, may play a general role in resistance by releasing elicitor-active molecules from pathogens (Yoshikawa cited in Keen 1993).

The potential number of resistance mechanisms in a host is large, as demonstrated by studies of tomato (*Lycopersicon esculentum*) resistance to *Cladosporium fulvum* (Hammond-Kosack and Jones 1994). A large number of *Cf* (*C. fulvum* resistance) genes have been bred into tomato from close wild relatives. All of these genes confer dominant resistance, but in a detailed study on the relative efficiencies of these and two other *Cf* genes, Hammond-Kosack and Jones (1994) demonstrated that dominance is not complete at most of these resistance loci. Instead, heterozygotes at each gene exhibited a delayed resistance reaction relative to that of homozygotes. Interestingly, resistance conditioned by different genes acted at different times during the infection process. Genes that acted earlier in infection restricted hyphal ingress into the mesophyll more than those acting later. Furthermore, resistance conditioned by earlier acting genes made resistance at later acting genes irrelevant. Finally, in comparison to resistance expressed in the parental *L. esculentum* genome, each *Cf* gene was less effective when expressed against a hybrid *L. esculentum* × *Lycopersicon pennellii* F1 background, indicating that interaction with other components of the genome also influences resistance phenotype. Of course, tomato cultivars evolve primarily in response to artificial selection. However, the level of complexity involved in the transmission of *Cf* resistance suggests that simple single gene models would be insufficient to accurately predict the evolution of this trait in wild relatives of tomato.

Mechanisms to increase mutation rates. Coevolutionary models predict that rare host genotypes should be resistant to common pathogen genotypes. By similar reasoning, novel pathogen genotypes should escape detection by common host genotypes. Thus selection should favor resistance and virulence genes with structures that promote high mutation rates. Studies in barley (*Hordeum vulgare*) and flax suggest that resistance against specific biotrophic fungi may involve complex genes within which unequal

crossing-over or some other mechanism of gene rearrangement can produce unusually high levels of mutation (Pryor 1987). A similar mechanism produces high levels of genetic variation for mating types in yeast (*Saccharomyces cerevisiae*) and surface antigens in trypanosomes (Borst and Greaves 1987), both systems in which rapid production of genetic variants is advantageous. The structure of the *avrBs3* gene in the bacterial pathogen *Xanthomonas campestris* pv. *vesicatoria* exhibits another mechanism for enhanced rates of evolution. This gene encodes a large protein with 17 repeated amino acid motifs in its central region (Bonas et al. 1989), and different deletion mutants exhibit different host specificities (Conrads-Strauch et al. 1993, Herbers et al. 1991).

Quantitative resistance. The breeding of resistance into crop plants has focused almost exclusively on resistance genes of major effect (Nass et al. 1981). Major resistance genes frequently produce dramatic levels of resistance to specific fungal genotypes, but evolutionary change in pathogenic fungi often defeats this resistance quickly. This phenomenon has led some plant breeders to look to polygenic resistance as a potential source of durable crop protection. Whereas major gene resistance produces categorical differences in resistance among individuals, polygenic resistance results in continuously distributed variation in resistance level.

Polygenic traits, also called quantitative traits, are generally assumed to be conditioned by the small additive effects of many alleles at many loci (Falconer 1981). There are many examples of polygenic resistance to phytopathogens (reviewed in Thompson and Burdon 1992). Recent efforts to estimate the number of genes involved in polygenic resistance have produced variable results. Pè and colleagues (1993) found at least five loci involved in resistance to *Gibberella zeae* infection in maize (*Zea mays*). In barley, variation in adult plant resistance to powdery mildew (*Erysiphe graminis*) has been attributed to additive and dominant effects of as many as five independent genes (Heun 1987). In oats (*Avena sativa*), four to nine genes have been postulated to be responsible for this trait (Jones 1986), while differences between winter wheat (*Triticum aestivum*) cultivars have been ascribed to as few as two or three genes (Das and Griffey 1994) or as many as 14 different chromosomes (Chae and Fischbeck 1979). Virtually nothing is known about the numbers of genes underlying quantitative resistance in natural plant populations. Moreover, there is little or no discussion in the literature of polygenic virulence in phytopathogens.

Instead of viewing polygenic resistance as a panacea for crop breeders, Nelson (1979) and others suggested that oligogenic resistance (conditioned by few genes of major effect) and polygenic resistance actually involve the same genes, but that the level of resistance that these genes produce is conditional on the internal and external genetic environment in which they are expressed. In particular, Nelson (1979) and others (Abdalla and Hermsen 1971, Arnold and Brown 1968) proposed that so-called defeated major resistance genes might still condition minor levels of resistance against virulent pathogen genotypes and that the cumulative effects of many archaic resistance genes are responsible for observed quantitative resistance.

Using methods developed to identify and map quantitative trait loci, several laboratories have sought empirical evidence with which to test this hypothesis. Some studies have produced corroborating evidence. For example, some major resistance genes in winter wheat that have been defeated by virulence genes in powdery mildew (*E. graminis* f. sp. *tritici*) still have a measurable ability to restrict the increase and severity of disease (Nass et al. 1981). Other studies have found correlations between major gene loci and quantitative resistance but have also revealed quantitative trait loci unlinked to known major genes (Freymark et al. 1993, Heun 1992). Apparently, defeated genes may contribute to polygenic resistance but do not completely explain all the variance in these traits.

Costs and benefits of resistance and virulence

In addition to being influenced by the mode of inheritance of resistance and virulence, the ecological and evolutionary outcome of host-pathogen coevolution is also likely to depend on whether these traits are involved in fitness trade-offs.

Durability of nonhost resistance and fitness costs of virulence. The degree of specificity of the complementary interaction between host and pathogen has been used to categorize resistance into two types: nonhost and race-specific. Nonhost resistance protects an entire plant species from infection by all members of a pathogenic taxon, whereas race-specific resistance protects only some members of a host species from only certain members of the pathogenic taxon. This distinction is of considerable economic significance because race-specific resistance is more easily overcome through pathogen evolution than is nonhost resistance. Breeding new resistant crop varieties is a costly and time-consuming task. Consequently, the length of time it takes the pathogen population to evolve virulence to the new resistance allele, commonly referred to as the durability of the allele, determines in part the economic value of the new variety.

Until recently, it was assumed that the genetic mechanisms underlying differential resistance among host species are distinct from those underlying resistance differences among genotypes within a species. However, recent work suggests that the dichotomy is artificial. Many aspects of the host responses of race-specific and nonhost resistance are similar, especially with respect to the mRNAs and protein products that accumulate as disease resistance is expressed (Hadwiger and Culley 1993). These results have led to a more general paradigm of the chemical signaling that conditions incompatibility in both nonhost and race-specific interactions. Within this framework, elicitors are categorized as either general or specific, depending on the taxonomic range of compatibility they condition. However, the general mechanisms by which

they elicit host resistance are assumed to be similar.

General elicitors are produced by an entire pathogen species or genus and induce resistance reactions in entire species of hosts. For example, all members of the fungal species *Phytophthora megasperma* produce glucans in their cell walls (Sharp et al. 1984). These glucans are potent elicitors of the hypersensitive response in all varieties of soybeans, but they are ineffective in parsley (*Petroselinum crispum*; Parker et al. 1991). In contrast to general elicitors, specific elicitors are found only in particular pathogen genotypes and function only in some plant cultivars within a host species (Keen 1993). For example, the *avr9* gene of the hemibiotrophic fungus *C. fulvum* encodes a small peptide that elicits the hypersensitive response in tomato plants possessing the complementary disease resistance gene, *Cf9* (Van den Ackerveken et al. 1992). Strains of the fungus without *avr9* successfully infect hosts with the *Cf9* resistance gene (Van den Ackerveken et al. 1992), raising an interesting question that pertains to all pathogen elicitors: Why do pathogens continue to produce compounds that stimulate host reactions that prevent or limit infection and thereby reduce pathogen fitness?

This question is important because it suggests that focusing on the interaction of elicitors with the host may be the wrong approach to understanding the relative durabilities of host and nonhost resistances. In fact, the term *elicitor* is an unfortunate historical artifact of this focus. The pathogen does not produce an elicitor to alert the host of its presence. Instead, an elicitor is some substance needed by the pathogen for normal metabolism (Thompson 1994). The function of these compounds in avirulence is a secondary development occasioned by the evolution in hosts of mechanisms that detect and respond to the pathogen. By readjusting our perspective, we can see that the taxonomic breadth of general elicitors may provide an important clue as to why resistance to them (nonhost resistance) is more durable. These insights can also be helpful in evaluating the potential for fitness costs of virulence.

In general, genes producing products fundamental to organismal fitness tend to be highly conserved among taxa (Kimura 1983). General elicitors are, by definition, shared by a wider taxonomic range of organisms than are specific elicitors. For example, oligosaccharide elicitors, such as glucans, which serve as general elicitors of soybean resistance against *Phytophthora*, are conserved across a wide taxonomic range and have even been purified from commercial yeast extract (Hahn 1981). Such a general distribution of oligosaccharide elicitors, even in nonpathogenic fungi, suggests that they make some essential contribution to fungal fitness. If general elicitors perform more essential functions (or their specific conformation is more critical to their function) in the pathogen than do specific elicitors, then host resistance genes that detect and respond to general elicitors should be more durable than those that complement more specific elicitors. Resistance genes that recognize general elicitors are likely to be more durable because mutations in the pathogen to halt production of these compounds would be more detrimental to microbial fitness. Thus, although various elicitors may function similarly in provoking the host hypersensitive response, the observation that resistance to general elicitors is more durable seems to have a plausible evolutionary explanation. This argument also suggests that virulence acquired by losing general elicitor function should involve substantial fitness costs.

There is, however, an alternative explanation for elicitor homology among taxa. Specifically, gene homology may arise from a common recent origin followed by lateral gene transfer. For example, several different variations on the *avrBs3* gene in *X. campestris* pv. *vesicatoria* have virulence activity in tomato and pepper (*Capsicum annuum*). Because of their sequence homology, and because in some cases they are flanked by long inverted repeat sequences, there has been speculation that the *avrBs3* genes evolved recently and have spread among bacterial taxa via lateral transmission (Bonas et al. 1993). If so, then the expectation that resistance to elicitors conserved across taxa should be more durable may mislead plant breeders and produce erroneous expectations about virulence costs.

The hypothesis that elicitors produced by *avr* genes make essential contributions to pathogen fitness was tested by Kearney and Staskawicz (1990), who demonstrated that the *avrBs2* avirulence gene plays an important role in fitness of the bacterial pathogen *X. campestris* pv. *vesicatoria*. Like the genes producing glucans in *Phytophthora*, *avrBs2* is highly conserved among several other *X. campestris* pathogen varieties (Kearney and Staskawicz 1990). These researchers found that when grown on a susceptible host, *avrBs2* mutant (virulent) strains had lower fitness than the avirulent wild-type strain. Furthermore, when avirulence was restored to the mutant strain by complementing it with a plasmid-borne copy of the wild-type avirulence gene, fitness was restored to near wild-type levels. Thus the product of the *avrBs2* gene makes a significant contribution to pathogen fitness, and loss of that product to achieve virulence involves a detectable fitness cost to the pathogen. However, this cost can be detected only when the pathogen is grown in culture or infects a susceptible host—a host lacking the ability to detect the *avrBs2* gene product.

Other studies have also found evidence that virulence is costly. Rouse and colleagues (1980) found that *E. graminis* forms virulent to wheat cultivars with one resistance gene exhibited reduced fitness relative to avirulent forms on cultivars lacking that resistance gene. In survey studies, a decline in the frequencies of particular virulence genes following reductions in the frequencies of the corresponding resistance genes may indicate that virulence is costly. Grant and Archer (1983) found an approximately 5% cost for possessing unnecessary virulence at the *Sr6* locus in *Puccinia graminis tritici* (wheat stem rust) and a similar cost of unnecessary virulence at the *Mla6* locus in *E. graminis*.

How do avirulence gene products contribute to pathogen fitness? Un-

fortunately, except for viral coat proteins, we do not know the function of avirulence gene products in the pathogens that produce them (Keen 1993). Nonetheless, it is interesting to speculate. Several proteinaceous elicitors have been characterized since the gene product of *avr9* was described in *Phytophthora*; all are small, cysteine-rich proteins (reviewed in Templeton et al. 1994). Templeton and colleagues (1994) reviewed the functions of similar proteins in both fungal and nonfungal species and used this information to speculate upon the possible function of the *avr* gene products in fungi. For instance, small, cysteine-rich proteins are important in the self-recognition necessary for sporophytic pollen self-incompatibility in *Brassica napus* (Dzelzkalns et al. 1992), suggesting that they might also be important in fungal self-recognition (Templeton et al. 1994). This hypothesis is particularly intriguing because it would also explain the intraspecific diversity of elicitors produced by the *avr9* gene. Self-recognition genes must have many loci so as to avoid false identification of conspecifics with the same self-recognition genotype as self.

Costs of resistance. Although introduction of resistance alleles into crop varieties is only rarely accompanied by yield penalties (Burdon 1987), some exceptions have been reported. For example, genes for resistance to crown rust that were introduced into cultivated oats (*Avena sativa*) from the wild red oat (*Avena sterilis*) were found to reduce grain yields (Simons 1979). Yield reductions were also observed in tobacco lines resistant to tobacco mosaic virus and *Fusarium* wilt (Chaplin 1970), although this study used conventional methods of tobacco culture, including removal of flowers and basal branches, which makes extrapolation of fitness from leaf yield questionable. Bergelson (1994) found that when protected from herbivores and fungi by pesticides, two lettuce cultivars resistant to leaf root aphid and downy mildew produced fewer flower buds than near-isogenic lines that lacked such resistance. Moreover, the magnitude of this cost differed between cultivars, indicating that the resistance trade-off is contingent on genetic background.

Some studies found increases in yields of cultivars with resistance alleles, even in the absence of disease. For example, two different genes for resistance to crown rust were each associated with increased yield in cultivated oats (Frey and Browning 1971). The effects of resistance on yield may vary with both the physical and the genetic environment. The magnitude by which resistance genes increased oat yield depended on the genetic background into which a gene was placed. In another study, temperature influenced the costs of resistance in the wild oat *Avena fatua* (Burdon and Müller 1987): In a warm greenhouse, genotypes susceptible to crown rust performed better than resistant genotypes; in a cold greenhouse the relationship was reversed. Bergelson and Purrington (in press) found that disease resistance involved fitness costs in 54% of 46 studies, 4 of which were mentioned above.

Summary on costs. The evidence suggests that costs of virulence are more common and perhaps of larger magnitude than costs of resistance. The reasons for this pattern seem clear: to become virulent, pathogens must often lose the function of conserved genes that are important to fitness. In contrast, specific resistance in the host plant is likely to involve the acquisition of function, such as production of receptors to detect pathogen growth. Such traits may involve allocation costs or entail deleterious alterations of previously functioning biochemical pathways (Simms 1992), but the magnitudes of such costs are likely to be less than those incurred by virulent pathogens. I would predict a different pattern, however, for cases in which virulence involves a gain of function, such as the production of toxins (Panaccione 1993). In this situation virulence might be less costly than resistance, especially when resistance involves modification and consequent loss or reduction of function of the molecular targets of microbial toxins.

Coevolution in natural plant populations

It has been suggested that gene-for-gene relationships between phytopathogens and crop hosts are an artifact of plant breeding procedures (Day et al. 1983) and may not be typical of interactions of pathogens with natural plant populations (Parker 1992). Several studies of natural plant populations have identified gene-for-gene relationships with pathogens (reviewed in Parker 1994), but so few studies have been done on natural populations that generalization is difficult.

Studies of natural plant populations have produced little evidence that disease resistance involves fitness trade-offs. In experiments designed to minimize the potential for bias due to genetic background in the hog peanut, *Amphicarpaea bracteata*, Parker and colleagues (Parker 1992, Parker and Wilkins 1990) found no evidence that genes for disease resistance were harmful in a disease-free environment. In fact, in the absence of disease, resistant hog peanuts had higher mean seed biomass than did susceptible plants. In the tall morning glory, *Ipomoea purpurea*, resistance to the hemibiotrophic fungal pathogen *Colletotrichum dematium* was not associated with any reduction in survival or flower or fruit production (Simms and Triplett 1994). This pattern is similar to that found for costs of resistance to insect herbivores in this species (Simms and Rausher 1987, 1989). Costs of resistance to herbivores do occur in natural populations of this plant, but they are often small in magnitude and are by no means ubiquitous (Simms 1992).

These results have motivated Parker (1992) to argue that high levels of genetic variation for pathogen resistance that are observed in natural plant populations may frequently be due to historical effects in nonequilibrial systems. However, because so few studies have been done on natural plant populations (e.g., we have no evidence regarding costs of virulence in pathogens on natural plant populations), it is too early to determine how often Parker's argument is correct.

Acknowledgments

This article was written while I was supported by a grant from the National Science Foundation (BSR-8918030). J. Bergelson, M. Ruddat, and P. Kotanen provided helpful comments on an earler draft. I thank L. Real for the invitation to participate in this special issue.

References cited

Abdalla MMF, Hermsen JGT. 1971. The concept of breeding for uniform and differential resistance and their integration. Euphytica 20: 351–361.

Anagnostakis SL. 1987. Chestnut blight: the classical problem of an introduced pathogen. Mycologia 79: 23–37.

Anderson RC. 1972. The ecological relationships of meningeal worm and native cervids in North America. Journal of Wildlife Diseases 8: 304–310.

Anderson RC, Prestwood AK. 1979. Lungworms. Pages 266–317 in Hayes F, ed. The diseases of the white-tailed deer. Washington (DC): US Fish and Wildlife Service.

Arnold MH, Brown SJ. 1968. Variation in the host-parasite relationship of a crop disease. Journal of Agricultural Science 71: 19–36.

Ausubel FM, Katagiri F, Mindrinos M, Glazebrook J. 1995. Use of *Arabidopsis thaliana* defense-related mutants to dissect the plant response to pathogens. Proceedings of the National Academy of Sciences of the United States of America 92: 4189–4196.

Bailey JA. 1991. Recognition events associated with specific interactions between plants and pathogenic fungi. Pages 210–224 in Smith CJ, ed. Biochemistry and molecular biology of plant-pathogen interactions. Oxford (UK): Oxford University Press.

Bailey JA, O'Connell RJ. 1989. Plant cell death: a determinant of disease resistance and susceptibility. Pages 275–283 in Graniti A, Durbin RD, Ballio A, eds. Phytotoxins and plant pathogenesis. Berlin (Germany): Springer-Verlag.

Bent AF, Kunkel BN, Dahlbeck D, Brown KL, Schmidt R, Giraudat J, Leung J, Staskawicz BJ. 1994. *RPS2* of *Arabidopsis thaliana*: a leucine-rich repeat class of plant defense resistance genes. Science 265: 1856–1860.

Bergelson J. 1994. The effects of genotype and the environment on costs of resistance in lettuce. American Naturalist 143: 349–359.

Bergelson J, Purrington CB. In press. Surveying patterns in the cost of resistance in plants. American Naturalist.

Bonas U, Stall RE, Staskawicz BJ. 1989. Genetic and structural characterization of the avirulence gene *avrBs3* from *Xanthomonas campestris* pv. *vesicatoria*. Molecular & General Genetics 318: 127–136.

Bonas U, Conrads-Strauch J, Balbo I. 1993. Resistance in tomato to *Xanthomonas campestris* pv. *vesicatoria* is determined by alleles of the pepper-specific avirulence gene *avrBs3*. Molecular & General Genetics 238: 261–269.

Borst P, Greaves DR. 1987. Programmed gene rearrangements altering gene expression. Science 235: 658–667.

Bryant JP, Tuomi J, Niemalä P. 1988. Environmental constraint of constitutive and long-term inducible defenses in woody plants. Pages 367–389 in Spencer KC, ed. Chemical mediation of coevolution. New York: Academic Press.

Burdon JJ. 1987. Diseases and plant population biology. Cambridge (UK): Cambridge University Press.

Burdon JJ, Chilvers GA. 1977. The effect of barley mildew on barley and wheat competition in mixtures. Australian Journal of Botany 25: 59–65.

Burdon JJ, Müller WJ. 1987. Measuring the cost of resistance to *Puccinia coronata* CDA in *Avena fatua* L. Journal of Applied Ecology 24: 191–200.

Chae YA, Fischbeck GW. 1979. Genetic analysis of powdery mildew resistance in wheat cultivar "Diplomat." Zeitschrift fur Pflanzenzuchtung 83: 272–280.

Chaplin JF. 1970. Associations among disease resistance, agronomic characteristics, and chemical constituents in flue-cured tobacco. Agronomy Journal 62: 87–91.

Conrads-Strauch J, Balbo I, Bonas U. 1993. Repetitive motifs in the *avrBs3* avirulence gene family determine specificity of resistance to *Xanthomonas campestris* pv. *vesicatoria*. Pages 37–40 in Frittig B, Legrand M, eds. Mechanisms of plant defense responses. Dordrecht (the Netherlands): Kluwer Academic Publishers.

Das MK, Griffey CA. 1994. Heritability and number of genes governing adult-plant resistance to powdery mildew in Houser and Redcoat winter wheats. Phytopathology 84: 406–408.

Day PR. 1974. Genetics of host-parasite interaction. New York: W. H. Freeman & Co.

Day PR, Barrett JA, Wolfe MS. 1983. The evolution of host-parasite interaction. Pages 419–430 in Kosuge T, Meredity CP, Hollaender A, eds. Genetic engineering of plants: an agricultural perspective. New York: Plenum Press.

de Wit PJGM. 1992. Molecular characterization of gene-for-gene systems in plant-fungal interactions. Annual Review of Phytopathology 30: 391–418.

DeBach P. 1974. Biological control by natural enemies. Cambridge (UK): Cambridge University Press.

Dinesh-Kumar SP, Whitham S, Choi D, Hehl R, Corr C, Baker B. 1995. Transposon tagging of tobacco mosaic virus resistance gene *N*: its possible role in the TMV-*N*-mediated signal transduction pathway. Proceedings of the National Academy of Sciences of the United States of America 92: 4175–4180.

Dwyer G, Levin SA, Buttel L. 1990. A simulation model of the population dynamics and evolution of myxomatosis. Ecological Monographs 60: 423–447.

Dzelzkalns VA, Nasrallah JB, Nasrallah ME. 1992. Cell-cell communication in plants: self-incompatibility in flower development. Developmental Biology 153: 70–82.

Fagerström T, Larsson S, Tenow O. 1987. On optimal defence in plants. Functional Ecology 1: 73–81.

Falconer DS. 1981. Introduction to quantitation genetics. 2nd ed. London (UK): Longman.

Fenner F, Myers K. 1978. Myxoma virus and myxomatosis in retrospect: the first quarter century of a new disease. Pages 539–570 in Kurstak E, Maromorosch K, eds. Viruses and environment: Third International Conference on Comparative Virology, Mont Gabriel, Quebec. New York: Academic Press.

Fenner F, Ratcliffe RN. 1965. Myxomatosis. Cambridge (UK): Cambridge University Press.

Fenner F, Woodroofe GM. 1965. Changes in the virulence and antigenic structure of strains of myxoma virus recovered from Australian wild rabbits between 1950 and 1964. Australian Journal of Experimental Biology and Medical Science 43: 359–370.

Fenner F, Day MF, Woodroofe GM. 1956. The epidemiological consequences of the mechanical transmission of myxomatosis by mosquitoes. Journal of Hygiene 54: 284–303.

Fenner F, Poole WE, Marshall ID, Dyce AL. 1957. Studies in the epidemiology of infectious myxomatosis. VI. The experimental introduction of the European strain of myxoma virus into Australian wild rabbit populations. Journal of Hygiene 55: 192–206.

Flor HH. 1955. Host-parasite interaction in flax rust—its genetics and other implications. Phytopathology 45: 680–685.

_____. 1956. The complementary genic systems in flax and flax rust. Advances in Genetics 8: 29–54.

Frank SA. 1993. Coevolutionary genetics of plants and pathogens. Evolutionary Ecology 7: 45–75.

Frey KJ, Browning JA. 1971. Association between factors for crown rust resistance and yield in oats. Crop Science 11: 757–760.

Freymark PJ, Lee M, Woodman WL, Martinson CA. 1993. Quantitative and qualitative trait loci affecting host-plant response to *Exserohilum turcicum* in maize (*Zea mays* L.). Theoretical and Applied Genetics 87: 537–544.

Gabriel DW. 1986. Specificity and gene function in plant-pathogen interactions. American Society of Microbiology News 52: 19–25.

Gow NAR. 1993. Nonchemical signals used for host location and invasion by fungal pathogens. Trends in Microbiology 1: 45–50.

Grant MW, Archer SA. 1983. Calculation of selection coefficients against unnecessary genes for virulence from field data. Phytopathology 73: 547–551.

Griffin GJ. 1992. American chestnut survival in understory mesic sites following the chestnut blight pandemic. Canadian Journal of Botany 70: 1950–1956.

Hadwiger LA, Culley DE. 1993. Nonhost resistance genes and race-specific resistance. Trends in Microbiology 1: 136–141.

Hahn MG. 1981. Fragments of plant and fungal cell wall polysaccharides elicit the accumulation of phytoalexins in plants. [Ph.D. thesis.] University of Colorado, Boulder, CO.

Hammond-Kosack KE, Jones JDG. 1994. Incomplete dominance of tomato *Cf* genes for resistance to *Cladosporium fulvum*. Molecular Plant-Microbe Interactions 7: 58–70.

Herbers K, Conrads-Strauch J, Bonas U. 1991. Race specific plant resistance to bacterial spot disease determined by repetitive motifs in a bacterial avirulence protein. Nature 346: 172–174.

Heun M. 1987. Combining ability and heterosis for quantitative powdery mildew resistance in barley. Plant Breeding 99: 234–238.

_____. 1992. Mapping quantitative powdery mildew resistance of barley using a restriction fragment length polymorphism map.

Genome 35: 1019–1025.
Jones IT. 1986. Inheritance of adult-plant resistance to mildew in oats. Annals of Applied Biology 109: 187–192.
Kearney B, Staskawicz BJ. 1990. Widespread distribution and fitness contribution of *Xanthomonas campestris* avirulence gene *avrBs2*. Nature 356: 385–387.
Keen NT. 1975. Specific elicitors of plant phytoalexin production: determinants of race specificity in pathogens? Science 187: 74–75.
_____. 1990. Gene-for-gene complementarity in plant-pathogen interactions. Annual Review of Genetics 24: 447–463.
_____. 1993. An overview of active disease defense in plants. Pages 3–11 in Fritig B, Legrand M, eds. Mechanisms of plant defense responses. Dordrecht (the Netherlands): Kluwer.
Kimura M. 1983. The neutral theory of molecular evolution. Cambridge (UK): Cambridge University Press.
Kolattukudy PE, Rogers LA, Li D, Hwang C-S, Flaishman MA. 1995. Surface signaling in pathogenesis. Proceedings of the National Academy of Sciences of the United States of America 92: 4080–4087.
Leonard KJ. 1977. Selection pressures and plant pathogens. Annals of the New York Academy of Sciences 287: 207–222.
Lindsay WP, Lamb CJ, Dixon RA. 1993. Microbial recognition and activation of plant defense systems. Trends in Microbiology 1: 181–187.
Long SR, Staskawicz BJ. 1993. Prokaryotic plant parasites. Cell 73: 921–935.
Martin GB, Brommonschenkel SH, Chungwongse J, Frary A, Grand MW, Spivey R, Wu T, Earle ED, Tanksley SD. 1993. Map-based cloning of a protein kinase gene. Science 262: 1432-1436.
May RM. 1983. Parasitic infections as regulators of animal populations. American Scientist 71: 36–45.
Mode CJ. 1958. A mathematical model for the co-evolution of obligate parasites and their hosts. Evolution 12: 158–165.
_____. 1961. A generalized model of a host-pathogen system. Biometrics 17: 386–404.
Moffat AS. 1994. Mapping the sequence of disease resistance. Science 265: 1804–1805.
Nass HA, Pedersen WL, Mackenzie DR, Nelson RR. 1981. The residual effects of some "defeated" powdery mildew resistance genes in isolines of winter wheat. Phytopathology 71: 1315–1318.
Nelson RR. 1979. The evolution of parasitic fitness. Pages 23–46 in Horsfall JG, Cowling EB, eds. Plant disease: an advanced treatise. Vol IV. New York: Academic Press.
Panaccione D. 1993. The fungal genus *Cochliobolus* and toxin-mediated plant disease. Trends in Microbiology 1: 14–20.
Parer I, Conolly D, Sobey WR. 1985. Myxomatosis: the effects of annual introductions of an immunizing strain and a highly virulent strain of myxoma virus into rabbit populations at Urana, New South Wales Australian Wildlife Research 12: 407–423.
Park T. 1948. Experimental studies of interspecific competition. I. Competition between populations of flour beetles *Tribolium confusum* Duval and *T. castaneum* Herbst. Ecological Monographs 18: 265–307.
Parker JE, Schulte W, Hahlbrock K, Scheel D. 1991. An extracellular glycoprotein from *Phytophthora megasperma* f. sp. *glycinea* elicits phytoalexin synthesis in cultured parsley cells and protoplasts. Molecular Plant-Microbe Interactions 4: 19–27.
Parker MA. 1992. Disease and plant population genetic structure. Pages 345–362 in Fritz RS, Simms EL, eds. Plant resistance to herbivores and pathogens: ecology, evolution, and genetics. Chicago (IL): University of Chicago Press.
_____. 1994. Pathogens and sex in plants. Evolutionary Ecology 8: 560–584.
Parker MA, Wilkins RT. 1990. Effects of disease resistance genes on *Rhizobium* symbiosis in an annual legume. Oecologia 85: 137–141.
Pè ME, Gianfranceschi L, Taramino G, Tarchini R, Angelini P, Dani M, Binelli G. 1993. Mapping quantitative trait loci (QTLs) for resistance to *Gibberella zeae* infection in maize. Molecular & General Genetics 241: 11–16.
Price PW. 1980. Evolutionary biology of parasites. Princeton (NJ): Princeton University Press.
Pryor A. 1987. The origin and structure of fungal disease resistance genes in plants. Trends in Genetics 3: 157–161.
Rice G, McCoy A, Webb T, Bond C, Speed V. 1980. Memories of the American chestnut. Pages 397–421 in Wigginton E, ed. Foxfire 6. Garden City (NJ): Anchor Press/Doubleday.
Rouse DI, Nelson PR, MacKenzie DR, Armitage CR. 1980. Components of rate-reducing resistance in seedlings of four wheat cultivars and parasitic fitness in six isolates of *Erysiphe graminis* f. sp. *tritici*. Phytopathology 70: 1097–1100.
Ryals J, Ward E, Metraux JP. 1991. Systemic acquired resistance: an inducible defense mechanism in plants. Pages 205–229 in Wray JL, ed. Inducible plant proteins: their biochemistry and molecular biology. Cambridge (UK): Cambridge University Press.
Ryals J, Lawton KA, Delaney TP, Friedrich L, Kessmann H, Neuenschwander U, Uknes S, Vernooij B, Weymann K. 1995. Signal transduction in systemic acquired resistance. Proceedings of the National Academy of Sciences 92: 4202–4205.
Saloniemi I. 1993. A coevolutionary predator-prey model with quantitative characters. American Naturalist 141: 880–896.
Scharloo W. 1964. The effect of disruptive and stabilizing selection on the expression of *cubitus interruptus* in *Drosophila*. Genetics 50: 553–562.
Seger J. 1992. Evolution of exploiter-victim relationships. Pages 3–25 in Crawley MJ, ed. Natural enemies: the population biology of predators, parasites and diseases. Oxford (UK): Blackwell Scientific.
Sharp JK, McNeil M, Albersheim P. 1984. The primary structures of one elicitor-active and seven elicitor-inactive hexa (B-D-glucopyranosyl)-D-glucitors isolated from the mycelial walls of *Phytophthora megasperma* f. sp. *glycinea*. Journal of Biological Chemistry 259: 11321-11336.
Simms EL. 1992. Costs of plant resistance to herbivory. Pages 392–425 in Fritz RS, Simms EL, eds. Plant resistance to herbivores and pathogens: ecology, evolution, and genetics. Chicago (IL): University of Chicago Press.
Simms EL, Rausher MD. 1987. Costs and benefits of plant resistance to herbivory. American Naturalist 130: 570–581.
_____. 1989. The evolution of resistance to herbivory in *Ipomoea purpurea*. I. Natural selection by insects and costs of resistance. Evolution 43: 573–585.
Simms EL, Triplett JK. 1994. Costs and benefits of plant responses to disease: resistance and tolerance. Evolution 48: 1973– 1985.
Simons MD. 1979. Influence of genes for resistance to *Puccinia coronata* from *Avena sterilis* on yield and rust reaction of cultivated oats. Phytopathology 69: 450–452.
Stevenson-Hamilton J. 1957. Tsetse fly and the rinderpest epidemic of 1896. South African Journal of Science 58: 216.
Stiling PD. 1992. Introductory ecology. Engelwood Cliffs (NJ): Prentice-Hall.
Templeton MD, Rikkerink EHA, Beever RE. 1994. Small, cysteine-rich proteins and recognition in fungal-plant interactions. Molecular Plant-Microbe Interactions 7: 320–325.
Tenhaken R, Levine A, Brisson LF, Dixon RA, Lamb C. 1995. Function of the oxidative burst in hypersensitive disease resistance. Proceedings of the National Academy of Sciences of the United States of America 92: 4158–4163.
Thompson JN. 1994. The coevolutionary process. Chicago (IL): University of Chicago Press.
Thompson JN, Burdon JJ. 1992. Gene-for-gene coevolution between plants and parasites. Nature 360: 121–125.
Thrall PH, Biere A, Antonovics J. 1993. Plant life-history and disease susceptibility—the occurrence of *Ustilago violacea* on different species within the Caryophyllaceae. Journal of Ecology 81: 489–498.
Tyler B. 1993. To kill or not to kill: the genetic relationship between a parasite and an endophyte. Trends in Microbiology 1: 252–254.
Van den Ackerveken GFJM, Van Kan JAL, de Wit PJGM. 1992. Molecular analysis of the avirulence gene *avr9* of the fungal tomato pathogen *Cladosporium fulvum* fully supports the gene-for-gene hypothesis. Plant Journal 2: 359–366.
Van der Putten WH, Troelstra SR. 1990. Harmful soil organisms in coastal foredunes involved in degeneration of *Ammophilia avenaria* and *Calammophila baltica*. Canadian Journal of Botany 68: 1560–1568.
Van der Putten WH, Van Dijk C, Peters BAM. 1993. Plant-specific soil-borne diseases contribute to succession in foredune vegetation. Nature 362: 53–56.
Van Riper C III, van Riper SG, Goff ML, Laird M. 1986. The epizootology and ecological significance of malaria in Hawaiian land birds. Ecological Monographs 56: 327–344.
van Valen L. 1973. A new evolutionary law. Evolutionary Theory 1: 1–30.
Warner RE. 1968. The role of introduced diseases in the extinction of the endemic Hawaiian avifauna. Condor 70: 101–120.
Wright S. 1969. Evolution and the genetics of natural populations. Vol. 2: the theory of gene frequencies. Chicago (IL): University of Chicago Press.
Yoshikawa M, Takeuchi Y, Horino O. 1990. A mechanism for ethylene-induced disease resistance in soybean; enhanced synthesis of an elicitor-releasing factor, β-1,3-glucanase. Physiological and Molecular Plant Pathology 37: 367–376.