PARASITE-HOST INTERACTIONS¹

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INTRODUCTION

The diversity of known strategies for parasitic life styles is truly astonishing. Many species of parasitic worms, for example, utilize only one host species, while others cycle between two or more (as many as four) different species of hosts. Some parasites are highly virulent, seriously debilitating or even killing their hosts, while others cause only minor damage. Some parasites (such as viruses) are very small relative to their hosts, and have the capacity for explosive reproduction. Others are almost as large as their hosts, and have relatively slow generation times. As such, parasites are difficult to categorize. Here I use "parasite" to refer to organisms that have an obligate association with, and a negative effect on, another organism (the host).

Host strategies for dealing with parasites are equally complex. Vertebrates have highly specialized immune systems that can rapidly respond to infection, and then store information that can be used to mount future responses to the same type of infection. Invertebrates lack the memory cells of true immune systems, but they do have complex self-nonself recognition systems for recognizing and killing foreign tissues. Plants also have highly specialized defenses against pathogens, and the genetic basis of these defenses is especially well known due to the work of plant pathologists on crop plants.

The myriad of details involved in the interactions between hosts and their parasites is overwhelming; but there are some shared, general aspects of these interactions that are of particular interest to evolutionary ecologists. First, parasites may attack in a frequency-dependent way. In other words, the probability of infection for a particular host genotype is expected to be, at least in part, a function of the frequency of
that host genotype. This expectation has implications for sexual selection and the evolutionary maintenance of cross-fertilization (Sakai, Chapter 11; Savalli, Chapter 14). Second, parasites may affect the population density of their hosts, and host density may feed back to affect the numerical dynamics of the parasite. Host density may also affect natural selection on the reproductive rates of parasites, which in turn is likely to affect host fitness and host dynamics. These issues can become quite complex, but they are nonetheless important for understanding the ecology and evolution of natural populations and the emergence of new diseases. In what follows, I provide examples that illustrate some of the more important ideas that are currently emerging from studies of parasite-host interactions.

CONCEPTS AND CASE STUDIES

Gene Frequency Dynamics: the Red Queen Hypothesis

Consider the fate of a very common host genotype in a population exposed to parasites. Assume that successful infection requires that the parasite precisely match the genotype of its host. Otherwise, the host recognizes the parasite as an invader and kills it. Parasite genotypes that can successfully infect (match) the most common host genotype will be favored by natural selection, and the associated alleles will spread in the population. If the parasite is sufficiently virulent, then evolutionary change in the parasite population will result in ever increasing selection against common host genotypes, eventually driving them down in frequency. When the frequency of the common host genotype is diminished, then some new, previously rare, host genotype becomes the most common one. This then provides a new target for the parasite
population, and the newly common host genotype is expected to be attacked in the same way, but by a different parasite genotype. This kind of coevolutionary interaction could easily lead to the cycling of both host and parasite allele frequencies (Fig. 1A); and, as such, it stands as a powerful mechanism for the maintenance of genetic diversity in natural populations. The technical term for this kind of interaction is “time-lagged, frequency-dependent selection,” which simply means that there is selection against common host genotypes and that this selection is lagged in time. The time lag is due to the fact that the parasites cannot instantaneously respond to changes in the host population. In fact, it may take several generations for the parasite population to “lock onto” the most common host type.

Such interaction between hosts and parasites is commonly referred to as an arms race, but this is a misleading analogy. An arms race involves an escalation in weaponry (from clubs to swords to guns to bazookas…), not a recycling of weapons. Yet it is precisely a recycling of types that concerns us here, so a more useful analogy is a chase. If you are chasing me, and I dodge to the right, you are forced to also dodge right; but your adjustment to my new direction will occur with a slight delay. Once you make this adjustment, I will dodge left, forcing you to also dodge left, but with another delay. And, even if you are faster, these delays mean you will stay slightly behind me. Note that neither of us changes weapons, we are just running: a leg race instead of an arms race. The important point here is that my dodge forces you, the parasite, to change course, which in turn causes me, the host, to change course and so on. In an important sense, then, even though both of us are running as fast as we can, neither of us are getting anywhere, although we are covering a lot of ground. This running as fast as we can
without getting anywhere is the gist of the Red Queen’s famous remark to Alice in *Through the Looking Glass* (Carroll 1872): *Now here, you see, you have to run as fast as you can to stay in the same place.* Hence, the idea that host-parasite coevolution can lead to oscillatory gene-frequency dynamics in both the host and the parasite has come to be known as the Red Queen hypothesis (Following Bell 1982).

In the analogy, a change of directions is analogous to the spread of a different, but not new, genotype in a polymorphic population. Now consider an asexual mutant in a large population of sexual hosts. Let us say that the mutant clone has an uncommon genotype, so it spreads. Because the mutant is asexual, it faithfully reproduces its genotype every generation, and it very quickly becomes common. Now, as above, there is selection on individuals in the parasite population to be able to infect this newly abundant host clone, at which point one of two things is expected: 1) The parasite drives the clone to extinction, or 2) The parasite drives the clone down to a point where it is rare, but not extinct, and then the clone begins to spread again due to its rare advantage. Either way, the parasite population has acted to keep the asexual host clone from replacing the sexual host population. This is a special case of the Red Queen hypothesis applied to breeding system evolution. According to this idea, parasites may impose selection on their hosts for sexual reproduction, and vice versa.

There is, however, one additional consideration. Clones, because they only produce daughters, have a much greater rate of intrinsic growth than the average of all the sexual females. In fact, the advantage is expected to be as much as two-fold, meaning the clone would initially double every generation. The question now becomes: can the parasite prevent the fixation of a clone with a two-fold reproductive advantage? In
theory, coevolutionary pressure from parasites can successfully prevent the clone from replacing the sexuals only if they kill or sterilize infected individuals (May and Anderson 1983). This is a lot to ask, even from a parasite. Most parasites are simply not that virulent.

Please note, however, the logical error. I implied that the theory is incorrect because most parasites don’t kill or sterilize their hosts. But the theory makes no prediction about what most parasites do. It only requires one “sufficiently virulent” parasite, or perhaps more likely, a combination of parasites. Further, the theory does not require that the parasite themselves kill or sterilize the host, only that they lead, directly or indirectly, to a catastrophic loss of host reproductive potential. How could that happen?

William Hamilton, who originally fleshed out the Red Queen hypothesis (Hamilton 1980), has also suggested (with R. Axelrod and R. Tansey) a solution to the virulence problem (Hamilton et al. 1990). Suppose, they imagined, that parasites track common host genotypes as suggested above. Suppose further that none of the different species has much of an individual effect, but the independent effects add up, so that a host with many species of parasites is somewhat sicker than a host with few parasites. Nonetheless, all the worms, fungi, bacteria, and viruses combined do not kill the host. Finally, suppose that the host competes for resources (which should be true most of the time), and that the least infected hosts are the best competitors. If, for example, the resource will only support 80% of the individuals in the population, then it is likely that a significant fraction of the 20% that fail to reproduce are also the most infected. In this example, parasites did not directly kill their hosts; they simply rendered the hosts less
able to compete in a very competitive world. Such a situation can lead to selection for sexual reproduction, even if the clones produce twice as many daughters as the sexual females. This is a very important idea, which also points to a large gap in present knowledge. We do not know the effects of infection on competitive ability for very many species.

As it stands, the Red Queen hypothesis is difficult to test, but progress has been made by examination of the assumptions. The most apparent assumption for Red Queen dynamics and the parasite theory of sex is the presence of rare advantage. Host genotypes that have been rare in the recent past should be less targeted by parasites than host genotypes that have been common in the recent past. Happily, this is a testable idea.

Rare advantage in clonal snails

A recent study of rare advantage was conducted on a clonal population of freshwater snails in New Zealand (Dybdahl and Lively 1998). We wanted to know two things: 1) do host clones oscillate over time in a way that is consistent with the Red Queen hypothesis? And 2) is there an advantage to being rare? To address the first question we plotted the change in frequency of clones against the time-lagged change in the prevalence of trematode infection in these same clones. So, for example, we plotted the change in host clones between years one and two against the change in infection between years two and three. We plotted these changes for a six-year study, reasoning that the Red Queen hypothesis predicted that the correlation should be positive, since parasites are expected to respond to host genotypes with a lag. We found that host clones oscillated over time; and, as anticipated by the theory, host clone changes were correlated with the lagged change in infection (Fig. 1B).
To test for rare advantage, we conducted a laboratory experiment at the end of the field study. The experiment tested whether host clones that had remained rare over the course of the study were also less susceptible to infection than clones that were common over the course of the study. We found that rare clones were indeed significantly less infected following experimental exposure to the local source of parasites (Fig. 2A). We then asked whether the rare advantage was due to being locally rare per se, or whether there were correlated traits associated with rareness that also made the rare genotypes less infectable (Lively and Dybdahl 2000). We reasoned that common clones may be common as a result of a greater competitive ability, but this ability to compete for resources might trade-off with resistance to parasites. Therefore, the most common clones might be more easy to infect, independent of any coevolutionary interactions. In a follow-up experiment, we used an outside source of parasites, one that was drawn from a different population of snails, which could not have been tracking the common clones in the original population we studied. We found that the outside source did not discriminate between rare and common clones (Fig. 2B). The local source of parasites, however, did again disproportionately infect the common clones. Hence, having a rare genotype, and not some correlated trait, conferred an advantage on the rare host clones, thus demonstrating frequency-dependent selection on the genes directly involved in the interaction. These results are also consistent with experiments showing local adaptation by these same trematodes (Lively 1989), and with field surveys that show a positive, significant correlation between the frequency of sexual individuals in a population and the risk of infection by trematodes (Lively 1992).
Multiple mating and parasite resistance in bee colonies

Another recent experimental study that supports the Red Queen theory was reported by the Swiss team of Boris Baer and Paul Schmid-Hempel (Baer and Schmid-Hempel 1999). In this study, they wanted to know the value to queens of mating with multiple males (polyandry). Multiple mating should produce a more genetically variable brood, which should result in fewer parasites. They worked with bumble bees, and they played the role of male bees by artificially inseminating queens with the sperm of either: 1) four brothers, to give a "low-diversity" broods (N = 12), or 2) four unrelated males, to give a "high-diversity" broods (N = 4). They then stored the queens for one month at 6°C to simulate winter before allowing them to start their first broods in the lab. Finally, they put the developing colonies into flowering meadows in the Swiss countryside.

The results were striking (Fig. 3). The intensity of infection (number of parasites in an infected individual) and the prevalence of infection (frequency of infected individuals within a colony) were both significantly lower in the high-diversity broods than in the low-diversity broods. Apparently, the worker bees were exposed to parasites while foraging. These parasites then spread once inside the colony, and the infection spread faster in colonies where the broodmates were expected, based on treatment, to be more closely related. Importantly, this expectation for relatedness was confirmed by direct analysis of molecular markers (P. Schmid-Hempel, personal communication); and the idea that disease transmission occurs more readily among related individuals was directly demonstrated for this bee species (Bombus terrestris) in a separate experimental study (Shykoff and Schmid-Hempel 1991). Hence, taken together, the results demonstrate that polyandry (mating with multiple unrelated males) reduces the spread of
disease within bumblebee colonies, and it may explain the occurrence of polyandry in many animal species.

The Baer and Schmid-Hempel (1998) study also showed that disease negatively affected the colonies’ production of fertile individuals. In fact, the high-diversity colonies produced about twice as many reproductive bees as the low-diversity colonies. Thus, there is direct experimental evidence showing that genetic diversity not only reduces disease, but also increases colony fitness. These results are entirely consistent with expectations under the Red Queen hypothesis; and they suggest that genetic diversification of offspring through outcrossing may be especially valuable when offspring are aggregated in colonies or litters (as suggested by Rice 1983).

Rarity and disease spread

The specific effect of host-genotype frequency on the spread of disease was elegantly shown in a study by Shamsul Akanda and Christopher Mundt (Akanda and Mundt 1996). They used four different cultivars of wheat, each of which were susceptible to different strains of rust (caused by a fungus). They planted the wheat cultivars in pairs, in five different ratios (10:90, 25:75, 50:50, 75:25, and 90:10) in a huge replicated experiment that was repeated for two years. They wanted to know how cultivar frequency would affect the spread and severity of the rust, so they inoculated the replicated field plots with different strains of the disease by transplanting infected seedlings into the plots. Here again the results were dramatic. The study showed that the severity of the rust increased significantly with cultivar frequency (Fig. 4). There was, therefore, an advantage to having a rare genotype in the face of the spreading disease. Interestingly, the plots in which two cultivars were planted in a 50:50 ratio had the lowest
average number of rust lesions per plant. This latter result demonstrates the value of mixing genotypes in agricultural situations, and it is further suggestive of the value of diversifying offspring by outcrossing.

Note that I have mixed two issues above concerning rare advantage that I now want to cleanly separate. One advantage stems from having a genotype that has a recent history of rareness, as in the snail study (coevolutionary rare advantage). The other advantage stems from having a rare genotype during the spread of a disease, as in the wheat study, independent of coevolutionary effects (epidemiological rare advantage). In nature, both coevolutionary rare advantage and epidemiological rare advantage would be expected to be very important, and it is easy to imagine that epidemiological rare advantage would fuel the coevolutionary process (see also Thompson, Chapter 23).

*Parasites and Population Dynamics*

In the previous section, we were interested in the effects of parasite-host interactions on gene frequencies. We turn now to conceptually similar issues, but ones that focus on population dynamics, rather than gene-frequency dynamics. We are also interested in whether host density affects the transmission of parasites and the stability of parasite populations.

It seems clear that the density of susceptible hosts should affect the transfer of parasites between hosts, as in the rust study just discussed. Exactly how this should occur, however, is less intuitive. Fortunately, the process can be modeled; and the parameters of the simple model have intuitive appeal. One of these parameters is the reproductive rate of the parasite ($R_0$), which we can think of as the number of infections generated by each infected host. If this value is less than one, then the parasite cannot
spread in the host population; if the value is greater than one, the parasite will spread at an exponential rate, at least initially.

Here is the basic model (taken from a review by Hesterbeck and Roberts 1995).

The rate of change \( \frac{dI}{dt} \) in the number of infected individuals in the population depends on the number of susceptible individuals in the population \( S \), times the number of infected individuals in the population \( I \), times the probability of contact between an infected and uninfected individual \( \beta \), all divided by the total host population size \( N \).

This gives:

\[
\frac{dI}{dt} = \frac{\beta SI}{N}.
\] (1)

If infected hosts become resistant at a certain rate due to acquired immunity, we must subtract that rate \( \gamma \) times the number of infected individuals \( I \). This gives the rate of change in the number of infected individuals as:

\[
\frac{dI}{dt} = \frac{\beta SI}{N} - \gamma I.
\] (2)

If we now introduce a small number of infected individuals in the population at time zero \( I_0 \), then \( S = N \), and \( I = I_0 \), and we get:

\[
\frac{dI}{dt} = \beta I_0 - \gamma I_0 = I_0(\beta - \gamma).
\] (3)

The disease will spread if the rate of change is positive, which requires only that \( \beta > \gamma \), or equivalently:

\[
\frac{\beta}{\gamma} > 1.
\] (4)

Hence, in this model, the basic reproductive rate, \( R_0 \), is the transmission coefficient divided by the recovery rate; the disease will spread if the former is greater than the later.
Continued spread of the disease is more restrictive, because, as individuals become infected, they are no longer susceptible to new infection. Thus the current reproductive rate, $R_c$, given $S$ susceptible hosts, $R_c(S)$, must be greater than one for the epidemic to continue spreading, where $R_c(S) = R_0S/N$ (which is simply $R_0$ times the frequency of susceptible hosts in the population).

The recovery rate ($\gamma$) is an interesting parameter. It makes one wonder what would happen if, by vaccination, a proportion of the population were to become “recovered” even before the disease began to spread. To see this effect in the model, we simply need to weight the number of susceptible individuals ($S$) by the frequency of individuals that have not been vaccinated ($1 - v$), where $v$ is the frequency of vaccinated hosts. Thus in equation 1, we replace $S$ with $S(1 - v)$. Now the rate of change in the number of infected individuals becomes:

$$\frac{dI}{dt} = \frac{\beta S(1-v)I}{N} - \gamma I. \quad (5)$$

As above, $S = N$ and $I = I_0$ at the beginning. Hence:

$$\frac{dI}{dt} = I_0[\beta(1-v) - \gamma]. \quad (6)$$

The disease will now spread in the partially vaccinated population when

$$\frac{\beta}{\gamma} (1-v) = R_0(1-v) > 1. \quad (7)$$

Note that the conditions for spread of the disease are now more restrictive, because the parasite’s reproductive rate ($R_0$) is multiplied by the fraction $(1-v)$. If $v$ is very high (near one) then the disease is extremely unlikely to spread. Hence there are two reasons to have a vaccination against the next flu: one is so that you do not get the flu, and the other is so that the pool of susceptible individuals is reduced, thereby reducing the chance
of an epidemic. In the present model, we would want to vaccinate enough individuals so that

\[ v > 1 - \frac{1}{R_0} \]  

(8)
in order to prevent the initial spread of infection.

*Population cycles in red grouse*

If an epidemic does occur, there are a few possible outcomes. One is that the host population is driven to extinction. Another is that the host population decreases in size, but is not driven extinct. In this latter case, if the number of susceptible hosts is driven below the threshold value for parasite spread \([R_c(S)<1]\), then the parasite will begin to die out (at least locally). This would then allow the host population to increase again, which suggests the potential for oscillatory population dynamics, analogous to that seen in Red Queen models of gene-frequency dynamics (Fig. 1A). Under theory, such oscillations in population size are more likely if infection has a much greater effect on the fecundity than on mortality (Dobson and Hudson 1992; May and Anderson 1978). Cyclical population dynamics have been observed in red grouse in Scotland since 1977, with population crashes about every 4-8 years. These crashes were associated with high levels of nematode (round worm) infections, which cause significant reductions in reproductive output (Hudson et al. 1992). The question is: do the worms cause the cycles, or are they just along for the ride? In 1989, Peter Hudson, Andy Dobson and Dave Newborn treated four of six populations of grouse with an anthelmintic (Hudson et al. 1998). They did not treat every individual, but they were able to treat 15-20% of the breeding populations, thereby decreasing the number of susceptible individuals. In 1993, they repeated the
treatment in two of these four populations. They cleverly picked these years (1989 and 1993) because they were predicted to be crash years. If the parasites were causing the crashes of red grouse, a crash would be expected in the two control populations, but not in the four treated populations. This is exactly what they found. The two untreated control populations crashed in '89 and '93, exactly as expected; but the populations treated in both '89 and '93 did not crash (Fig. 5). One of the populations treated once (in 1989) showed a small dip in that year, but nothing of the magnitude of the two control populations. This is striking experimental evidence that parasites can regulate host population size as well as cause host populations to cycle in a predictable way.

The Evolution of Virulence

Earlier, I mentioned the possibility that parasites might decimate their host populations to the point of extinction. This assertion may seem unlikely at first, because the parasites would also become extinct in the process. Thus, it might seem, that parasites should be selected to become increasingly benign, perhaps to the point of becoming commensal with their hosts, or even mutualistic. This way of reasoning formed a kind of "conventional wisdom" in the medical community until very recently (Ewald 1994).

Recent theories on the evolution of parasite virulence have shown that the conventional wisdom was incorrect. Natural selection does not operate according to long-range visions of what is best for the population, but rather by culling out genotypes that are less suited to present environmental conditions [a process that works best, in general, when the effective population size ($N_e$) times the selection coefficient ($s$) is much greater than one: $N_es \gg 1$]. Why should this be any different for parasites? Individuals
that have the highest probability of successful propagation into the next generation would be favored, independent of the long-range consequences. As you might expect, selection on the rate of parasite reproduction should be affected by the density of susceptible individuals in the host population.

The first biologists to dismember the previously popular conventional wisdom were Roy Anderson, Robert May, and Paul Ewald (Anderson and May 1982; Ewald 1983). The theory that they (and their followers) have developed relies on some basic principals of life-history evolution (see also Roff, Chapter 7). The basic idea is that the intrinsic rate of growth ($R_0$) for a parasite depends on a trade off between making many propagules in the host (e.g. lots of viruses) and the damage this causes to the host (Fig. 6). If, for example, the parasite propagates so fast that it kills the host, then there is selection to reduce the rate of propagule production (i.e., become less virulent). In this case, the conventional wisdom is right, but for the wrong reason. If on the other hand, the pathogen produces only a few propagules, but without any effect on the host, then it will surely be replaced by a strain that makes more propagules. This kind of reasoning suggest that parasite virulence should evolve to an intermediate level, but “intermediate” is somewhat vague. What it really means is that parasite virulence should evolve to the point where the marginal gains in fitness due to propagule production are equal to the marginal losses in fitness due to host mortality. This balance should depend on the parasite’s life cycle and the probability of transmission to the next host. This probability will depend on the local density of susceptible hosts.

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2This is a simplified view, because it does not take into account the variance in fitness. High variance in fitness might discount the propagule production as a way of bet hedging. Similarly, the simplified view does not take interactions with other parasites into account, which might select for higher virulence. Finally, the simplified view does not take into account any effects of parasite population structure.
Consider, for example, a virus of insect larvae that is only transmitted by causing the host to explode (Myers 1993). In this case, parasite transmission is coupled with host death, so the virus should pack as many virions as possible into the larva before causing the larva to splatter its contents into the environment. These contents, mostly virus, are picked up by other larvae, and transmission is accomplished. Viruses that did not kill the host would have a selective disadvantage. So much for the idea that parasites should evolve to be benign.

There are, of course, less extreme examples, but the basic idea holds: parasite populations should evolve under natural selection for individuals that maximize their own reproductive success, without regard to the host’s future. And, in some cases, such evolutionary change could lead to the host’s extinction. Along these lines, Van Valen (1971) has shown that some clades have declined in species number at a constant rate over evolutionary time. One way this could happen, he suggests, is that there is a reasonably constant probability that tight coevolutionary interactions go haywire, perhaps due to the evolution of hypervirulent parasites. This reasoning lead Van Valen to the original formulation of the Red Queen hypothesis, which was concerned with the rise and fall of clades (macroevolution) rather than alleles (microevolution). It is difficult to know whether the idea is correct, but it is nonetheless very interesting. Parasite virulence would be expect to increase under selection whenever the probability of transmission increases. Does this happen at a constant rate in evolutionary time?

Virulence theory, like most evolutionary theories, is difficult to directly test; but researchers can go after the critical assumptions. The conceptual core of the current theory on the evolution of virulence rests on two critical assumptions: 1) that higher rates
of replication in the parasite lead to greater reductions in host survivorship; and 2) that higher rates of replication in the parasite lead to a higher probability of transmission to the next host (Fig. 6). These assumptions were examined in an elegant study by Margaret Mackinnon and Andrew Read of Edinburgh University (Mackinnon and Read 1999). They injected one of eight different isolates of rodent malaria (*Plasmodium chabaudi*) into different groups of inbred mice. They then measured the replication rate of the parasite, the effect of infection on each mouse, and the proportion of mosquitoes that became infected after taking a blood meal from infected mice. Their results showed that replication rate was significantly different among the parasite strains, and that these differences were genetically based. In addition, replication rate was positively correlated with virulence, meaning that mice infected by parasite strains having high rates of replication were also more anemic. Finally, replication rate was significantly and positively correlated with the probability that the infection was transmitted to mosquitoes. Hence, both of the critical assumptions of the model were shown to be true.

*Catastrophic Disease in Natural Populations*

From the above, it may seem as if only two things matter to the spread and evolution of disease: gene frequencies and population density. This, of course, is not true. Here I illustrate, using a few examples, the effects of climate and habitat on the evolution and ecology of host-parasite interactions. This makes the situation more complex, but also more realistic.

One example involves a seastar (*Heliaster kubinijii*) in the Gulf of California. Prior to the summer of 1978, the rocky intertidal shores of this region were packed (up to
1/m³) with these voracious predators of barnacles, mussels, and many species of snails. This animal was already well known as a possible “keystone predator” due to its role in promoting local species diversity by eating whatever was most common. During a two-week period in June of 1978, however, *Heliaster* was virtually wiped out throughout the Gulf of California by a bacterial disease. What happened? How could such a common species become instantaneously so rare?

The most sensible explanation for the epidemic is that it had something to do with the exceptionally high sea surface-temperature during the summer of 1978, due to a particularly severe El Nino (Dungan et al. 1982). The very warm water may have reduced or eliminated *Heliaster*’s ability to combat diseases on its epidermis. Alternatively, it may have made the disease more virulent than it would otherwise might have been. It may be dangerous to speculate about the effects of climatic change (experiments are hard here), but such widespread patterns cannot be ignored. An entire species spanning the entire 1000km stretch of the Gulf of California disappeared virtually overnight, suggesting at the very least that there is more to disease than genetics and host density (or the interaction between the two).

In a recent review, Jared Diamond makes a compelling historical case for the joint effects of ecology, epidemiology, and evolution in the spread of human disease to the Americas (Diamond 1998). First, he convinces the reader that diseases were as important, or more important, in the conquest of Native Americans as the superior weaponry of the European invaders. The statistics he gives are staggering. In 1520, smallpox was introduced into the Aztec population of Mexico by the Spanish. At the time, there were 20 million people, none of which had been exposed to anything similar
at anytime in their lives, nor had their ancestors. An epidemic quickly killed about half of the population, demoralizing the Aztecs. By 1618, the population was reduced to only 1.6 million, a reduction of 92%. Similarly, a Mandran tribe of 2000 people in the Great Plains of North America were reduced to only 40 survivors in less than a month by smallpox; and there are many other examples in Polynesia as well as the Americas.

Such devastation of human populations is heart wrenching and difficult to fathom, but one has to wonder why it occurred. Diamond asks several interesting questions along these lines. Why did it work this way, and not the reverse? Why didn’t the original inhabitants of the Americas give the Spanish invaders something equally deadly? And where did these European diseases come from? The hypothesis that Diamond gives combines ecology, epidemiology and evolution. First, the high densities of European populations (due to the development of agriculture) led to the conditions for the spread of highly virulent diseases, which could not be maintained in small nomadic populations (but, remember, there were 20 million Aztecs, so this cannot be the whole story). Second, the emergent diseases led to strong selection on European human populations, so that genetically resistant individuals, which could then develop immunity, were more likely to survive. The native Americas could not have been through the horrendous bouts of selection that accompanied the epidemics in Europe, and they did not have any way to develop immunity. So, when smallpox was introduced to the New World, it rapidly spread in the highly social, dense populations of peoples that descended from the original colonists of the region. This made it easier for the bearers of the disease to prevail over the peoples devastated by the disease.
But how did the Europeans first get the disease? Diamond suggest that it jumped from the domesticated animals that lived in close association with the peoples in Europe. As such, it would seem that the domestication of animals in Europe led indirectly to the devastation of the indigenous peoples of North and South America.

CONCLUSIONS AND FUTURE DIRECTIONS

Parasitism is a rich and complex subject that captures many of the important ideas in evolutionary ecology (e.g., life-history evolution, trade offs, frequency- and density-dependent selection, kin selection, and breeding-system evolution). For evolutionary ecologists, there are vast opportunities (and many unanswered questions), and vast numbers of potential study systems. The most exciting part of the research to come lies in the diversity of interactions, and weaving together the effects of genetics and ecology under field conditions. This weave may or may not lead to general rejection of the atomized view of infection gained by the isolated search for resistance genes; but it will nonetheless lead to important discoveries and a much better understanding of one of the important forces of evolutionary and ecological change.

Several aspects of disease would at this point seem to especially merit additional study. One of these aspects is the effect of infection on the competitive ability of hosts, which is important for two reasons. One is that, if diseases, which might otherwise be considered avirulent, significantly reduce the ability of their hosts to compete for resources, then the Hamilton et al. (1990) modification of the parasite theory of sex is greatly strengthened. In one such study of the effect of rust infection on jewelweed (*Impatiens capensis*), we found that rust infection had no effect on the growth rate of plants in the wild when conspecific competitors were experimentally removed (Lively et
al. 1995). Hence, it would seem that the disease, by itself, was not having much of an
effect on plant fitness. But, infected plants grew at a significantly slower rate than
uninfected plants under the natural conditions of high plant density. There was thus an
interaction between infection and plant density of the kind required by the Hamilton et al
(1990) model. More experiments of this kind are needed to know whether the result is
general.

A second reason for understanding the effect of disease on the competitive ability
of infected individuals relates to the structure of communities. There is a rich literature
on the effects of predators on the structure of communities, especially in rocky intertidal
zones, but corresponding studies for the effects of parasites are relatively rare. One
example of a very nice study was recently published by Keith Clay and Jenny Holah
(Clay and Holah 1999). They found in a four-year field experiment that an association
with a fungal endophyte increased the competitive dominance of a grass (*Festuca
arundinacea*), which led to a decrease in local plant diversity. In other words, the
presence of an endophyte in one host species altered the structure of the entire
community. These kinds of effects may be very common, but, at present, there are very
few studies of the effects of diseases on the structure of communities.

Another gap in present knowledge concerns the genetic basis for infection.
The results from plant pathology suggest that gene-for-gene interactions determine
whether infection will occur, but less is known about natural populations. At present,
there is an interesting debate as to whether the results of plant pathology can be
extended to the natural world. The details of the genetic architecture turn out to be
critical to models of host-parasite coevolution, but there are insufficient data to know the answer.

Finally, there would seem to be considerable promise to fusing the genetics of Red Queen models with the ecological perspective of the epidemiological models (following May and Anderson 1983). The mathematics of these models could get quite gnarly, but there would nonetheless seem considerable potential to the effort.

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LITERATURE CITED


Carroll, L. 1872. Through the looking glass and what Alice found there. Macmillan. London, U.K.


Figure Legends

Fig. 1. The Red Queen hypothesis. The top panel (A) shows the results from computer simulation results of gene-frequency dynamics in a host-parasite interaction. The solid line gives the frequency of the AB genotype in a haploid host population; and the dashed line gives the frequency of infection in that same host genotype. The simulation model assumed that an exact genetic match was required for infection (e.g. parasite genotype AB can infect host genotype AB, but cannot infect host genotypes Ab, aB, or ab), and that there were two haploid loci with two alleles each (four genotypes). The model also assumed that hosts are exposed to one parasite propagule, and that successful infections reduce the host's fitness by 60%. Note that the infection curve is shifted 90 degrees to the right of the host-frequency curve. As such, a change in frequency of the host genotype AB is correlated with a time-lagged change in frequency of infection in that genotype. This leads to a testable prediction regarding dynamics in natural populations. Specifically, a change in frequency of a host-genotype should be correlated with the time-lagged change in infection of that same genotype. The bottom panel (B) gives a test of this prediction. Changes in frequencies of four common snail clones in Lake Poerua (South Island, New Zealand) are plotted against the time-lagged change in infection frequency for the years 1992 through 1996. The parasite (a trematode worm) causes complete sterilization of infected snails, and it infected 3-11 percent of the snail population during the course of the study. The significantly positive correlation (r = 0.748; P = 0.026) indicates that an increase in a host clone between years (e.g., 1992 to 1993) was followed by a
similar increase in infection of that clone in the following pair of years (1993-1994). Similarly, a decrease in infection of a snail clone was followed by decrease in infection in the following pair of years. This result is consistent with the Red Queen hypothesis. [Redrawn with permission from figure 4 in Dybdahl and Lively (1998)].

Fig. 2. Results of an experimental infection experiments comparing common clonal genotypes against rare clonal genotypes from Lake Poerua (South Island, New Zealand). The top panel (A) gives the results from an experiment conducted in 1996. Common clones (open circles) were significantly more infected as a group than the group of 40 different rare clones (closed circles) ($X^2 = 41.39; df = 1; P < 0.0001$). Clones were designated as "common" if they exceeded 15% of the population during at least one year during the four-year period prior to the experiment. Clones were individually designated are "rare" if they did not exceed 5% of the population during the four-year period prior to the experiment. [Redrawn with permission from figure 5 in Dybdahl and Lively (1998)].

The bottom panel (B) shows the results from similar infection experiment conducted in 1997. In this repeat of the 1996 experiment, the infection rate of common clones (open symbols) was compared with the infection rate in rare clones (closed symbols) for both sympatric parasites from Lake Poerua (circles) and allopatric parasites from a distant lake (Lake Ianthe, squares). Note that the sympatric parasites infected rare and common clones more than the remote source of parasites. Note also that the local, sympatric parasites infected common clones
more than rare clones (as observed in 1996) ($X^2 = 14.81; \text{df} = 1; P < 0.0001$), but the allopatric parasites did not infect common clones more frequently than the rare clones ($X^2 = 2.06; \text{df} = 1; P < 0.1517$). This result suggests that the common clones were more infected by the sympatric parasites due to coevolutionary interactions, rather than some inherent physiological characteristic of the common clones. [Redrawn with permission from figure 2 in Lively and Dybdahl (2000)].

For both figures, vertical bars give one binomial standard error; and the horizontal dashed line gives the average infection rate for the four common clones.

Fig. 3. Selected results, from the bumblebee study in Switzerland, comparing infection and reproduction in colonies having high genetic diversity versus low genetic diversity. Top panel (A) shows the prevalence of infection by a microsporidian parasite (*Nosema*); the difference between treatments was highly significant ($P = 0.01$). A different parasite, the trypanosome (*Crithidia bombi*), showed the same trend, but was not significantly different between treatments ($P = 0.12$; data not shown). Middle panel (B) shows the intensity of infection for the microsporidian parasite (*Nosema*), which was highly significantly different between the low- and high-diversity treatments ($P = 0.006$). Intensity of infection was significantly different and in the same direction for *Crithidia* ($P = 0.006$; data not shown). The bottom panel (C) gives the mean number of males produced in the high- and low-diversity treatments, which is a measure of the reproductive output of the colonies. The difference between these means is statistically significant ($P = 0.028$). Vertical bars are 1 standard error about the mean.
Fig. 4. Selected results from the wheat-rust study showing the relationship between the frequency of two cultivars (Jacmar [top panel, A] and Tyee [bottom panel, B]) and the severity of rust infection in plots that contained mixtures of these same two cultivars in different frequencies. Severity was defined as the percent of leaf area covered by rust lesions. In both cases, the relationship between cultivar frequency and disease severity was highly significant (P < 0.001). Similar results (not shown) were gained for these same two cultivars at a different site in the same year (1993) and in the following year (1994). Similar results were also gained for different pair-wise comparisons of cultivars, so the result was robust to the changes in cultivar composition as well as site and year of the experiment.

[Redrawn with permission from figures 1 and 3 in Baer and Schmid-Hempel (1999)].

Fig. 5. Cycling in red grouse in Scotland. The top panel (A) shows the number of red grouse in two populations that were not treated with an anthelmintic, which kills the parasitic nematodes of the grouse. Note that both populations crashed in 1989 and 1993. The middle panel (B) shows the results for two grouse populations that were treated for nematodes in 1989. Note that these two populations did not crash in 1989, as did the controls, but they did crash four years later in 1993. The bottom panel (C) shows the results for two populations that were treated for nematodes in both 1989 and 1993. Note that these populations did not crash at
any time during the course of the study. [Redrawn with permission from figure 2 in Hudson et al. (1998)].

Fig. 6. Illustration of ideas underlying the evolution of virulence. The top panel (A) shows the number of parasites in surviving hosts at time $t$ as a function of the population growth parameter, $\lambda$. The exponential increase was calculated from the standard equation for population growth: $N_t = N_0 \lambda^t$, for $N_0 = 1$ and $t = 5$.

The middle panel (B) shows host survivorship as a function $N_t$, where the effects of parasites are independent [survivorship = $(1-s)^N$, where $s$ gives the effect of each individual parasite]. The bottom panel (C) shows the products of the curves in A and B, which gives parasite fitness as a function of $\lambda$. The analytical solutions for $\lambda$ that maximizes parasite fitness is given in each panel as a solid circle. Note that host survivorship at this maximum is quite low, suggesting a highly virulent parasite at equilibrium.
Fig. 1
Fig. 2

Experimental infections (1996)

Experimental infections (1997)

Common clones

Rare clones

A

B

C

D

clones

clones

clones

clones
Fig. 3
Fig. 4

A

Disease severity on Jacmar

Frequency of Jacmar cultivar

B

Disease severity on Tyee

Frequency of Tyee cultivar
Fig. 5
Fig. 6