Host-Parasite Coevolution and Sex

Do interactions between biological enemies maintain genetic variation and cross-fertilization?

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Most eukaryotic organisms reproduce by cross-fertilization, at least during some part of their life cycle. Given the costs incurred by cross-fertilization, this pattern indicates that there is some general advantage associated with meiosis and genetic exchange. Conversely, it would seem that there must be some severe disadvantages associated with the various kinds of uniparental reproduction, such as parthenogenesis and self-fertilization.

This article fleshes out some of the recent ideas on parasite-mediated selection for cross-fertilization. At the heart of this subject is the idea of time-lagged, frequency-dependent selection. Natural selection of this kind is just as the name implies—selection against common genotypes but with a delay. Such selection is likely to be common in interactions between biological enemies such as parasites and their hosts. Parasites are under strong selection to infect the most common host genotypes, but because they cannot instantaneously track genetic changes in the host population, there is likely to be a lag in time. This kind of interaction can easily lead to sustained oscillations in host and parasite gene frequencies and hence the maintenance of genetic variation (Clarke 1976, Hamilton 1993, Hutson and Law 1981). It might also lead to selection for cross-fertilization (Bell 1982, Hamilton 1980, 1982, Jaenike 1978) and mate choice (Hamilton 1982, Hamilton and Zuk 1981).

A short-term advantage to sex is required if it is to persist in populations where reproduction through uniparental means is a possibility

The oscillations generated by time-lagged selection resulting from host-parasite interactions can be thought of as a jog around an oval track. Although a great deal of distance can be covered on such a track, one never really gets far from the starting point, and the average location does not vary much after only one lap. The same may be true for host-parasite interactions. If any particular host type becomes common, then parasites are under strong selection to be able to infect it. Once this happens, the host type is driven down in frequency, provided parasites have a significant, negative effect on host fitness. When host and parasite gene frequencies are plotted over time, the interaction is expected to look like two sine waves (one for the host and one for the parasite) that are 90° out of phase with each other (see Figure 1a; Nee 1989). If, instead, host and parasite gene frequencies are plotted against each other, the result looks like the oval track (Figure 1b). This constant cycling around a track is reminiscent of the Red Queen's remark to Alice in *Through the Looking Glass* after the two of them have been running for a long time without getting anywhere: "Now, *here*, you see, it takes all the running *you* can do, to keep in the same place" (Carroll 1871). And so it is true in host-parasite interactions: It is not a unidirectional, so-called arms race but rather a constant cycling that is expected under time-lagged, frequency-dependent selection. It is for this reason that parasite-mediated selection for cross-fertilization has been called the Red Queen hypothesis (following Bell 1982).

Two queens, both red

Actually there are two Red Queen hypotheses. Van Valen (1973) recognized the similarity between the Red Queen's world, where "it takes all the running *you* can do, to keep in the same place" (Carroll 1871), and coevolution between biological enemies on a macroevolutionary time scale. He suggested that coevolutionary interactions might account for the constant extinction rates observed in many taxa. Hence, species involved in antagonistic coevolution had to run as fast as they could to keep from going extinct.

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Even so, the interaction could go awry with a certain probability, leading to a constant level of extinction.

The second Red Queen hypothesis is a microevolutionary hypothesis about the effects of time-lagged, frequency-dependent selection and the maintenance of genetic variation (as illustrated in Figure 1). A special case of the microevolutionary Red Queen is that time-lagged, frequency-dependent selection could favor sex over parthenogenesis and perhaps cross-fertilization over biparental inbreeding and self-fertilization. In this article, I focus on the microevolutionary Red Queen as it relates to the maintenance of cross-fertilization.

Selection for cross-fertilization

The cost of sex. There is now widespread agreement that there is a so-called cost to cross-fertilization, but there is still some debate regarding the exact nature of the disadvantage. The easiest way to see the cost is to consider a rare female in a dioecious (having male and female reproductive organs on different individuals) sexual population that reproduces by obligate parthenogenesis. Assuming no concomitant reduction in fecundity, the parthenogenetic female is likely to produce twice as many daughters and four times as many granddaughters as the average sexual female (Charlesworth 1980, Maynard Smith 1978). Unchecked, the resulting clone is likely to recruit faster than the sexual subpopulation and rapidly replace it if resources are limited. In fact, for a population of 1 million sexual individuals, such replacement is likely to take place in less than 50 generations (see Figure 2). Therefore, for sex to be maintained in competition with parthenogenesis, it must have an advantage that is manifested within tens of generations.

This competitive advantage in parthenogenetic clones is the easiest way to see the cost of sex, which is unambiguously due to the production of males by sexual females (Maynard Smith 1978). It is harder to envision the cost of biparental sex in simultaneous hermaphrodites that produce mixtures of selfed and outcrossed progeny within a single brood. The cost of biparental sex in hermaphrodites can be due to either investment of resources in male function or reduction in relatedness between offspring and the maternal parent (Williams's [1975] so-called cost of meiosis), the outcome depending on how resources are allocated to the uniparental progeny (Lively and Lloyd 1990). In any case, as argued by Williams (1975), a short-term advantage to sex is required if it is to persist in populations where reproduction through uniparental means is a possibility. Based on the results in Figure 2, short term here would mean within tens of generations, depending on population size.

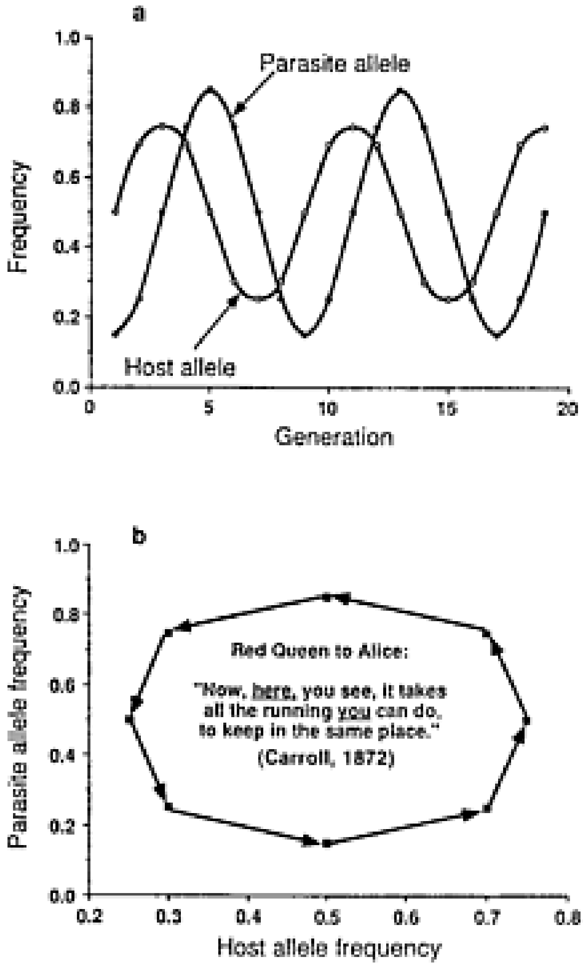

Figure 1. Parasite-mediated, time-lagged, frequency-dependent selection plotted over time (a) and as a phase diagram (b). In (a) the host and parasite curves are plotted as being 90° out of phase, following Nee (1989).

Hypotheses for the advantage of sex. The arguments for the short-term advantage of sex may be divided into two groups: genetic hypotheses and ecological (or adaptive variation) hypotheses. Genetic hypotheses seek to explain the maintenance of biparental sex in terms of the advantages of recombination, independent of the production of variable offspring. For example, Muller's (1964) and Kondrashov's (1988) ideas both have to do with the advantage that sexuals have over asexuals in clearing the lineage of deleterious mutations. Such hypotheses, however, do not account for the well-known distribution patterns of parthenogenetic plants and animals (Bell 1982). In general, parthenogenesis is more common at high latitudes and high altitudes; it is also more common in freshwater environments than in the sea and in disturbed habitats in general (reviewed in Bell 1982). The genetic theories could perhaps account for these patterns if finding a mate in these environments were difficult or impossible. Under such conditions it would always be better to reproduce by uniparental means to assure reproduction. This idea is the essence of the reproductive assurance hypothesis, which has been put forward to explain the distribution of parthenogenesis in plants (review in Bierzychudek 1987). The mutation-accumulation hypotheses might also explain the geographic correlates of parthenogenesis if mutation rates were higher at low altitudes and latitudes, in marine habitats and undisturbed areas.

The ecological hypotheses, by contrast, assume a direct advantage to producing variable offspring in variable environments (Weismann 1889). These arguments may be categorized according to whether they rely on frequency-dependent selection (i.e., rare advantage), and, if so, how the frequency dependence is generated (Figure 3). Under the hard-selection hypotheses, biparental sex is maintained by unpredictable changes in the physical environment. The short-term advantage of cross-fertilization under this model (the lottery model) lies in the production of variable offspring, one or more of which may be able to survive in the new environment (Williams 1975). For the lottery hypothesis, there is no advantage to being rare per se; but there is an advantage to producing variable young. The advantage comes from reducing the among-year variation in offspring survival.

Under the soft selection (density-dependent rare advantage) hypothesis, biparental sex is maintained by intraspecific competition in a physically stable environment. The advantage to cross-fertilization under this model lies in the production of rare offspring, which experience reduced competition for resources. This idea is supported by polymorphism theory (the theory on the maintenance of genetic polymorphism; Levene 1953, Maynard Smith 1962, 1970), although the conditions for multiple-niche polymorphism seem somewhat restrictive (Lively 1986, Maynard Smith and Hoekstra 1980). Bell (1982) refers to the idea as the tangled bank hypothesis, and he reasons that selection that maintains polymorphism could also favor biparental reproduction if the cost of sex is not too high (see also Case and Taper 1986, Ghiselin 1974, Koella 1988). Vrijenhoek (1979, 1984) put forward a similar idea, which he called the frozen niche–variation hypothesis, because the clones effectively freeze out genotypes from those available in the ancestral sexual population.

Finally, under the (microevolutionary) Red Queen hypothesis, cross-fertilization is maintained by selection resulting from interactions between biological enemies (Bell 1982, Bremermann 1980, Glesener and Tilman 1978, Hamilton 1980, Jaenike 1978, Levin 1975, Lloyd 1980, Price and Waser 1982). Outcrossing and recombination are favored because they allow for the production of rare offspring that are expected to have a greater chance of escaping parasites. Hence, as in the tangled bank hypothesis, selection is frequency-dependent in the Red Queen model, but the inherent time lags generated by parasites produce dynamics that are not expected under the tangled bank hypothesis.

Contrasting the alternatives in freshwater snails

One of the difficulties in testing the alternative ideas is that nature offers limited opportunities for direct comparison of parthenogenetic and sexual reproduction. One excellent organism for comparing the predictions of the different theories for sex is the dioecious freshwater snail, *Potamopyrgus antipodarum*. This snail occurs at high densities in freshwater habitats throughout New Zealand, and it is the molluscan host for several species of parasitic trematodes (MacArthur and Featherston 1976, Winterbourn 1973). In addition, the results of recent isozyme studies showed that some populations contain mixtures of sexual and parthenogenetic individuals and that the clonal lineages share unique alleles with the local sexual population, and hence are likely to be locally derived from and ecologically similar to the coexisting sexual population (Dybdahl and Lively 1995). The isozyme results were also consistent with the suggestion by Wallace (1992) that the clones are triploid and with the finding by Phillips and Lambert (1989) that parthenogenesis in this species is ameiotic. Finally, the results showed that clonal diversity within the mixed (sexual and clonal) populations is high, with up to 30 or more clones detectable using six polymorphic loci.

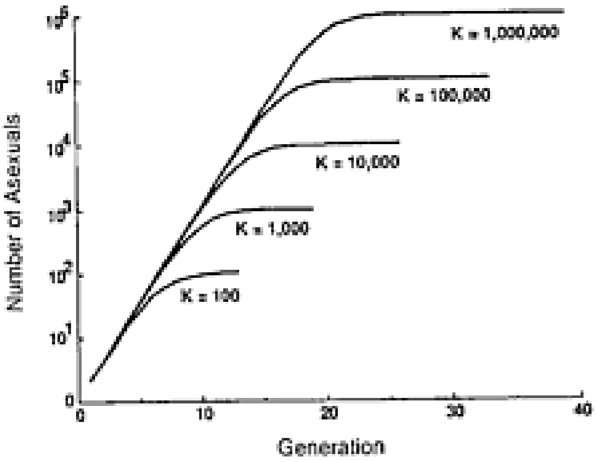

Figure 2. How long is short-term selection for sex? One way to measure the interval is to determine the number of generations required for a clone beginning with one individual to replace a sexual population of K individuals. Short-term selection for sex must be manifested within this period or the sexual population is likely to be eliminated. The figure gives the number of generations until the elimination of an obligately sexual population by a clonal population as a function of carrying capacity (K) of the population. The curves were calculated by iteration of the equation $P_t + 1 = P_t xk / [P_t + (1 - r)S_t]$, where P_t is the number of parthenogens at time *t*. The iterations began with the number of sexual individuals (S_t) set equal to $K - 1$, and they assume that male frequency in the sexual population (r) is 0.50 and that the relative fitness of parthenogens (x) is unity. The end point of each curve indicates extinction of the sexual population, operationally defined here as there being less than two sexual individuals remaining in the population. The main point of the figure is that the selective advantage of producing variable progeny must be manifested on the order of tens of generations if biparental reproduction is to persist.

To contrast the ecological hypotheses for the maintenance of sex in the snail, in 1985–1986 I collected *Potamopyrgus* from lakes and streams throughout the recently glaciated region of New Zealand's South Island. Making the assumption that, due to periodic flooding, streams are more physically unstable than lakes[1] (Winterbourn et al. 1981), the lottery hypothesis predicts more sexual reproduction in streams. The tangled bank hypothesis, by contrast, predicts that sex should be more common in lakes, where competition is expected to be greater. The Red Queen hypothesis predicts that sex should be positively related to the frequency of infected individuals, independent of habitat type.

The results of this survey were most consistent with the Red Queen hypothesis (Lively 1987). Lake populations contained a greater proportion of sexual individuals, as anticipated under the tangled bank model, but this outcome seems to be the result of greater parasitic pressure within lakes. Parasites explained more of the variation in sex ratio than did habitat per se. In fact, parasites explained a significant fraction of the variation within habitats. The most convincing evidence is that, when parasites were rare in either habitat, parthenogenesis was more common. Hence it would appear that parthenogens have been successful in replacing sexual individuals in areas where parasites were rare, as expected under the Red Queen hypothesis.

A more detailed survey focusing exclusively on lake populations of *Potamopyrgus* was also consistent with the Red Queen hypothesis but inconsistent with the reproductive assurance hypothesis (Lively 1992). There was no indication that par-

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[1] C. M. Lively, personal observation.

thenogenesis is negatively correlated with population density, as would be expected if sex were favored independent of parasites (and had only lost out where encounters with mates were rare). Thus there is no indirect support for the genetic hypotheses for sex, which rely on selection for reproductive assurance to explain the ecological correlates of parthenogenesis. It could be argued, however, that the observed positive correlation between sex and parasites is due to a greater infectivity of sexual individuals. This case seems unlikely if all else were truly equal, but the *Potamopyrgus* parthenogens were recently discovered to be triploid (Wallace 1992), and perhaps triploid individuals are for some reason more difficult to infect than sexual individuals. However, in field samples from populations containing sexual and clonal snails, there is no indication of a greater resistance to infection by the triploid clones.[2] In addition, it is difficult to understand how sexual populations could be correlated with sterilizing parasites if they were more prone to infection; clones should simply replace their sexual progenitors under these conditions, and the correlation would evaporate. Hence the simplest explanation is that parasites have prevented clones from replacing sexual populations in those areas where the risk of infection is high.

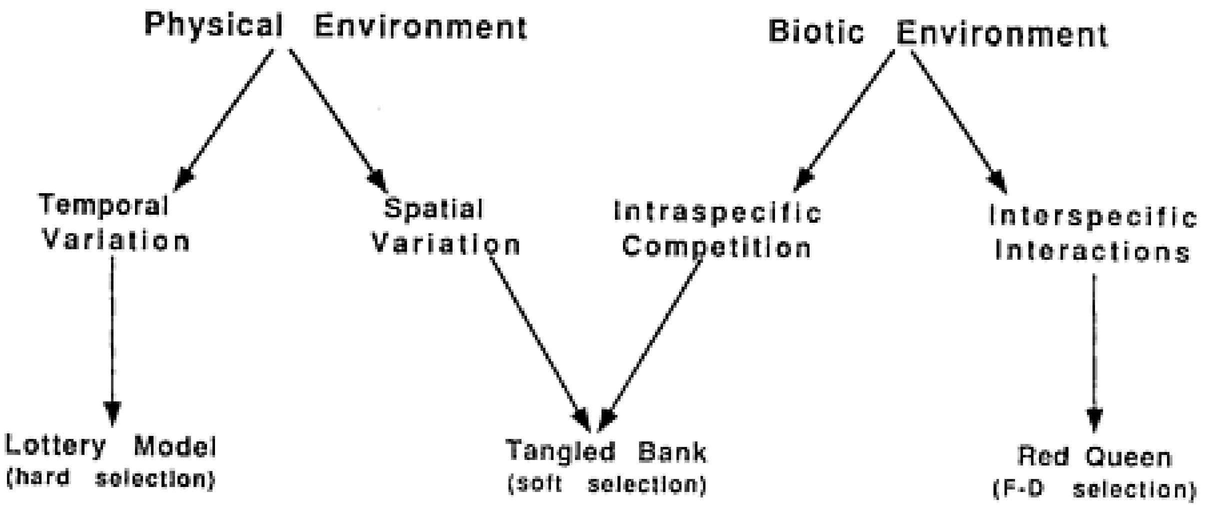

Figure 3. Flow diagram of the ecological hypotheses for the maintenance of biparental sex, showing how the different hypotheses are related. Note: F–D is used to mean frequency-dependent selection.

More recently, in 1994 Jukka Jokela and I examined the distribution of parasites and male *Potamopyrgus* in a single lake on the South Island of New Zealand. This lake (Lake Alexandrina) is a wildlife preserve, and it has abundant waterfowl. Our original purpose was to determine the extent of spatial variation for trematode infection in the lake, which was high (Jokela and Lively 1995a). But, in addition, we found that sex was correlated with trematode infection, exactly as for the between-lake surveys reviewed above (Jokela and Lively 1995b). Male *Potamopyrgus* were more common in the shallow-water habitats, from 0–1.5 meters deep, which is also where the final hosts (ducks) for many of the trematodes spend most of their time. Infection prevalence was also highest in these shallow areas. Hence it appears that cross-fertilization in the snail may have been selected in shallow waters as a direct result of the habitat preferences of the final hosts and that sexual individuals have been displaced by clonal females in deeper waters (to 7 m), where the risk of infection is much lower. Such a scenario requires that there is little migration by clonal snails, which seems to be the case based on the distribution of clones and their association with depth-stratified habitats (Fox et al. in press).

A similar correlation between parasites and cross-fertilization was recently reported for a Nigerian snail, *Bulinus truncatus* (Schrag et al. 1994a). This snail is a simultaneous hermaphrodite, but there are nonetheless two sexual morphs. One morph is euphallic, and, as the name implies, it has a penis and is capable of inseminating conspecifics. The other morph, however, is aphallic. The aphallic morph cannot inseminate other individuals, but it can and does self-fertilize if no euphallic morphs are around. As it turns out, the euphallic condition is induced by temperature in areas where the seasonal risk of parasitism is high, and it seems that the shift to euphally and cross-fertilization is appropriately timed so that an outcrossed brood is released when the risk of parasitism is highest (Schrag et al. 1994b). These results are remarkably consistent with expectations under the Red Queen hypothesis. They may also have important medical implications; the parasite *Schistosoma mansoni* is the cause of a devastating human disease, schistosomiasis.

Local adaptation by digenetic trematodes

If parasites are tracking common host genotypes, they should become locally adapted to their sympatric or so-called home host population. Parasites should then be better able to infect hosts from the same location than hosts from distant locations.

The results from reciprocal cross-infection experiments using the most common trematode (*Microphallus* sp.) of *P. antipodarum* were consistent with the local adaptation hypothesis (Lively 1989). In the initial experiment, snails and trematodes were taken from lakes on opposite sides of the Southern Alps in New Zealand, and the trematodes from both lakes were found to be better able to infect snails taken from the same lake. These snail populations were morphologically different and unlikely to have been exchanging migrants; it is also unlikely that the parasites, which have waterfowl for their final host, were being transported between the lakes. Hence both host and parasite populations would be expected to have diverged, and the reciprocal cross-infection experiment was consistent with this expectation. In a second experiment, parasites were taken from three lakes on the west side of the Alps, two of which were separated by only 7 km.

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[2] J. Jokela, C. M. Lively, M. F. Dybdahl, and J. A. Fox, 1995, submitted manuscript. Department of Biology, Indiana University, Bloomington, IN.

The results of this second experiment were also consistent with expectations under the local adaptation hypothesis: Parasites from all three lakes were best at infecting snails from the same lake. But, surprisingly, there was not much difference in the ability of the parasites to infect snails taken from the adjacent lake relative to the more remote lake 100 km to the southeast. Thus there was no hint of a gradient in adaptation by the parasites. They were simply better at infecting hosts from the same lake rather than any other lake, regardless of distance.

Similar results were recently found for another digenetic trematode living in lakes near the Swiss Alps (Ballabeni and Ward 1993). *Diplostomum phoxini* has a three-host (snail-fish-bird) life cycle. Host fish and parasites were taken from two lakes 35 km apart. The results of reciprocal cross-infection experiments showed that parasites taken from both lakes were more successful at infecting fish taken from the same source lake. Hence, like the New Zealand trematode, this parasite is locally adapted to infect its home host population. Here, however, the host is the second intermediate host. Even more recently, Manning et al. (1995) found using similar cross-infection experiments that schistosomes from two locations in Zimbabwe are locally adapted to their local snail populations. So far, local adaptation seems to characterize snail-trematode interactions, and it hints at an underlying coevolutionary dynamic.

There is also evidence for rapid evolutionary change by digenetic trematodes in response to changes in the local host population (Lively et al. 1990). These trematodes, which cause black-spot disease in the Mexican topminnow (*Poeciliopsis*), were found to be infecting the most common clonal type in two populations that contained mixtures of sexual and asexual individuals. But in a third pool the worms were disproportionately infecting the sexual population, even though one clone was abundant. However, Robert Vrijenhoek had been following these populations, and he knew that the highly infected sexual population was also highly inbred (see Vrijenhoek 1993). In 1983 he introduced 30 sexual and genetically variable fish collected upstream into the inbred population. Two years later the parasites were found to be disproportionately infecting the clone; the infusion of genetic variation was enough to give the previously inbred sexual fish the same advantage that their outcrossed conspecifics had enjoyed in the other two pools. In addition, where the fish were outcrossed, the sexuals had a lower mean but higher variance for infection (Lively et al. 1990); this result strongly indicates the existence of genetic variation for resistance, which is a requirement for the Red Queen hypothesis. Direct evidence for heritable resistance to infection by trematodes comes from a recent genetic study by Grosholz (1994).

Bugs in the parasite theory of sex?

In spite of the empirical support for a coevolutionary theory of sex, there are at least two potential theoretical difficulties for the Red Queen hypothesis. First, in order for parasites to promote sex over parthenogenesis, the effects of parasites must be severe. In fact, if parasites do not kill their hosts, it is unlikely that they will prevent the replacement of a sexual population by a clone with a twofold reproductive advantage (May and Anderson 1983). For the snail examples presented above, the parasites effectively killed infected hosts by sterilizing them; however, sterilization is not a common effect of parasites. If the Red Queen hypothesis is a general explanation for the maintenance of sex, the requirement of severe effects by parasites needs to be addressed.

A second difficulty is that parasites do not select for sexual reproduction per se. They select instead for diversity, however generated. Therefore, a sufficiently diverse set of clones should be able to replace a sexual population. In recent computer simulations, two clones were able to replace a sexual population of 1000 individuals where resistance to parasites was coded at two diallelic loci, giving four possible genotypes (Lively and Howard 1994). The parasites had to match exactly the host genotype for infection to occur, and the fitness of infected individuals was reduced to 70% of that of uninfected hosts. Under these conditions, the sexual population could coexist in a dynamic oscillation with a single clone. But, following entry of the second clone, the sexual population was replaced within tens of generations. Interestingly, the same result was observed when a third diallelic locus was added to the model, giving eight possible genotypes in the interaction. Hence it seems clear that the clonal population need not saturate the genetic possibilities exhibited in the sexual population in order to eliminate the sexual population.

Rank-order truncation selection. One idea that deals with both of these difficulties was recently presented by Hamilton et al. (1990). They suggested that parasites may exacerbate the effects of intraspecific competition to produce a severe effect on the fitness of infected hosts. Suppose, for example, that nest sites are a limiting resource and that there is intense competition among birds for the available sites. Suppose further that only the healthiest individuals are successful at securing these sites and that the remaining individuals simply fail to reproduce. Finally, let there be a number of parasites and pathogens of these birds that have additive effects on their health. So, for example, a bird infected with three species of parasites is less healthy than a bird infected with only two species of parasites. It is easy to imagine then that the birds infected with the most parasites are unlikely to successfully compete for the limited number of nest sites and therefore fail to reproduce. Hence the parasites are indirectly responsible for the reproductive failure of the most infected individuals. This kind of parasite-mediated truncation selects against the most infected birds, even if the effects of infection are otherwise minor. This idea seems to be a mixture of the soft selection proposed in the tangled bank hypothesis and the strict frequency-dependent selection of the Red Queen hypothesis.

Hamilton et al. (1990) used computer simulations to test this idea. They simulated populations of 200 individuals in which only 186 were able to reproduce. These individuals were exposed to a variable number of parasites (between two and six) in which infection occurred when the parasites matched the host genotype exactly at either one or two loci (depending on the simulation) for each of the parasite species. The 14 individuals in the runs of the simulation infected with the most species of parasites failed to reproduce. The remaining individuals produced the same number of offspring, independent of their levels of parasite infection. The results of these simulations showed that sexual individuals were favored over parthenogenetic individuals, provided there were more than two parasite species. Furthermore, the rank-order truncation selection prevented the accumulation of clonal diversity. Extensions of this model have shown that the results generally hold even in metapopulations of hosts and parasites, unless hosts tend to outdisperse their parasites, thereby preventing them from tracking common genotypes within populations (Ladle et al. 1993).

The dynamics of the selection process can be seen as follows. A novel clone is spun off from the sexual population with a randomly selected genotype. The clone has a twofold reproductive advantage, so it begins to spread. But as the clone becomes common, all species of parasites are under strong selection to be able to infect it, and eventually the clone is pushed back down in frequency. At some point the clone is rare again, but before it can recover its previous rare advantage, all of the members of the clone fall into the group of 14 individuals that fail to reproduce due to the truncation selection. The clone is thus driven to a rare frequency in the population. It does not, however, recover its rare advantage and begin to increase again, because the parasites overshoot and drive the clonal genotype to diminish in frequency even when rare.

The ratchet and the Red Queen. Another possible solution involves another combination of models: Muller's ratchet and the Red Queen. Muller's ratchet, one of the genetic models, would not operate fast enough to provide a short-term advantage to sex (see Figure 2), and it does not explain the distribution of parthenogens. But in combination with parasites this model could provide an effective mechanism for eliminating clones.

Muller's ratchet is easy to understand by analogy. Imagine a man with 50 shirts. Each shirt has ten buttonholes, but the actual number of buttons is variable, with a mean of seven. Let us assume that each morning the man randomly selects a shirt to wear and that there is a small chance that he will lose a button during the day. (Losing a button is analogous to mutation, where the loss of one button is one mutation.) Let us assume further that there is a small chance that the man will lose his shirt. (Losing a shirt is analogous to the chance that an individual will fail to reproduce due to a random event, such as an avalanche.) In order to keep the number of shirts the same, the man has to randomly select a shirt from his remaining stock, and the lost shirt is replaced with a shirt having the same number of buttons as the randomly selected shirt. Hence, and this is the key point, if the man loses his last shirt with ten buttons, it cannot be replaced with a shirt with ten buttons. The effect of this combination of button loss and shirt loss is that the mean number of buttons in the shirt collection has to decrease. Conversely, the mean number of empty buttonholes (mutations) has to increase. The only stable state here is a population of 50 shirts, all with zero buttons. This situation represents an asexual world, where the ratchet is likely to work to reduce the mean number of buttons until there are no buttons on any shirt. In a sexual world, by contrast, lost buttons can be taken from other shirts (in a process analogous to meiotic recombination). Thus if the last shirt with N buttons is lost, another shirt with N buttons can be created, thereby preventing the ratchet from clicking.

Thus the ratchet works by drift in small populations. Imagine that a clonal lineage is really composed of many different clones with a normal distribution of deleterious mut tions. It is then easy to see (as Mull [1964] first did) that all the indi viduals in the class with the fewe mutations might fail to reproduc by chance alone. That class woul then be eliminated, and it could n be reconstituted by recombinatio it is also extremely unlikely that could be recovered by back mut tion. Hence the ratchet clicks for ward one notch. This process result in an ever-increasing mutational loa and the eventual elimination of th clonal population, especially whe the population is allowed to declin in number as the mutational loa increases (Lynch and Gabriel 1990)

Parasites can interact with th ratchet by driving the clonal popu lation through the bottlenecks tha occur as a result of the time-lagge selection against common genotype (Figure 1a). Each time a clone i driven through a bottleneck, the rat of mutation accumulation due t the action of the ratchet is increased (It is as if parasites periodically re duce the number of shirts, making i more likely that the last shirt wit ten buttons is lost.) Computer simu lations have shown that adding th ratchet to parasitized population greatly increases the range of condi tions under which a sexual popula tion is resistant to replacement by single clone. Most important, sex i evolutionarily stable in population attacked by nonlethal parasites, eve when the probability of contact wit parasites is substantially less tha 100% (Howard and Lively 1994) In addition, the combination o Muller's ratchet with the time lagged, frequency-dependent selec tion imposed by parasites render sexual populations resistant to re placement by multiple coexistin clones (Lively and Howard 1994) Therefore, adding mutation accu mulation in clonal lineages to th effects of parasites would seem t help overcome two of the majo theoretical difficulties of the Re Queen hypothesis.

Time-lagged, frequency-depen dent selection, however, would no be required for clonal extinction Any sort of extreme oscillation in population could have the same effect in expediting the accumulatio of mutations in clonal competitor

(Lively and Howard 1994). Periodic deadly epidemics, for example, could lead to the extinction of clones without appeal to either genetic matching or frequency-dependent selection. In this case, the entire population (including clonal and sexual individuals) is depressed; but whereas the genetic load would accumulate in the clonal subpopulation with each additional epidemic, it would not accumulate in the sexual subpopulation. This kind of fluctuation would lead to the extinction of clonal competitors. Populations with chaotic population dynamics (May 1976) might also be expected to show a similar interaction with Muller's ratchet. Nonetheless, time-lagged selection by parasites should be a reliable source of bottlenecks for clonal genotypes. Keeping in mind that a clone can eliminate a sexual population in tens of generations (Figure 2), this consideration would seem to be important.

Parasites and mixed mating. Whether or not parasites are responsible for sex in the world, it is easy to see the logic of the theory. Any clone that becomes common should become disproportionately infected in the near future, and if the effects of the parasites are severe enough (in combination with mutation and/or resource competition), the clone should be beaten back and perhaps eventually eliminated from the population. It is harder to see, by contrast, how parasites might prevent the spread of an allele for self-fertilization. Such an allele would be quickly embedded in multiple genetic backgrounds, making it harder for parasites to track it, even when common. Nonetheless, the consequence of successive generations of selfing would be to reduce the genetic variation for disease resistance, which could give a frequency-dependent advantage to cross-fertilization. Strategy models that assume that the risk of parasite attack increases with the frequency of selfing show that mixtures of selfed and outcrossed offspring (mixed mating) can be evolutionarily stable over a wide range of values for inbreeding depression (Lively and Howard 1994). Hence attack by parasites could lead to conditions that favor the production of at least some outcrossed offspring.

Conclusion

Host-parasite interactions can lead to sustained oscillations in gene frequencies in both host and parasite populations, and such interactions potentially favor the production of genetically variable progeny over the production of invariant progeny.

There is empirical support for this theory from studies of snails and their trematode parasites, but more studies are required before meaningful decisions can be made. There are also some theoretical difficulties with the parasite (or Red Queen) theory of sex. These difficulties, however, diminish when the effects of parasites are considered in concert with either competition for resources or mutation accumulation in asexual lines.

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