CHAPTER 11

PARASITES AND SEX

Jon Seger and W. D. Hamilton

INTRODUCTION

Parasites of many kinds have long been recognized as important regulators of population size (e.g., May, 1983b), but only during the last decade or two have they been widely viewed as the protagonists in fast-paced (and long-running) evolutionary thrillers involving subtle features of the biochemistry, anatomy, and behavior of their hosts. On this view, their power as agents of evolution derives from their ubiquity and from the great amounts of mortality they can cause (which are also the properties that make them effective agents of population regulation) and, just as importantly, from their *imperfect* (but improvable) abilities to defeat the *imperfect* (but improvable) defenses of their hosts. Thus each party is expected to experience the other as a changeable (and generally worsening) part of its environment. In principle, prey and predator species have the same kind of relationship. But predators usually have generation times as long or even longer than those of their prey, while parasites may have generation times many orders of magnitude shorter than those of their hosts. If this asymmetry allows parasites to evolve improved methods of attack much faster than their hosts can evolve improved methods of defense, then the hosts' best defense may be one based on genotypic diversity, which, if recombined each generation, can present to the parasites what amounts to a continually moving target (e.g., Haldane, 1949; Levin, 1975; Glesner and Tilman, 1978; Jaenike, 1978; Bremermann, 1980, 1985; Bremermann and Pickering, 1983; Hamilton, 1980, 1982, 1986; Hamilton et al., 1981; Anderson and May, 1982; Bell, 1982, 1985; Price and Waser, 1982; Tooby, 1982; Rice, 1983).

In this chapter we discuss the idea that parasites may often play an important role in the maintenance of sexual reproduction. First, we distinguish the problem of maintaining full-fledged sex from that of maintaining genetic recombination in a species that always reproduces sexually. Then we describe the kinds of arguments and evidence that have been advanced to support the view that parasites may be uniquely able to generate the large selective differences that

are required to pay the "cost of sex" in most species. Finally, we discuss a few of the many specific predictions that can be derived from different versions of the host–parasite hypothesis. Whatever weaknesses this hypothesis may have, untestability does not seem to be one of them (see Levin et al., 1982).

We use the term "recombination" to mean the creation of new gametic associations of existing alleles at different loci, through the mechanisms of crossing over and reassortment of chromosomes. Because the nucleotide positions within a single functional gene can be viewed formally as separate loci, some forms of intragenic recombination are included in our definition. We use the term "sex" to mean nominally biparental reproduction involving differentiated male and female individuals or reproductive functions. This definition includes hermaphroditism, and even selfing, although selfing is in some respects a partial retreat from sex (as discussed more fully below).

Felsenstein (1985, and in this volume) argues that all ecologically motivated theories for the evolution of sex and recombination fall into one of two categories, depending on the cause of the maladaptive linkage disequilibrium to be lessened by recombination. Theories belonging to the Fisher–Muller category invoke random genetic drift, while those of the Sturtevant–Mather category invoke selection that periodically changes direction. Models of host–parasite coevolution show a generic tendency to cycle, or to move incessantly in some other, more complicated way, because any change that increases the average fitness of one species tends to lower the average fitness of the other (e.g., Person, 1966; Clark, 1976; Eshel and Akin, 1983). The idea that sex is a major weapon in the war against parasites would therefore seem to be an instance of the Sturtevant–Mather theory. But genetic drift caused by finite population size can also give rise to varying frequency-dependent selection mediated by parasites and thereby to an advantage for sex. Thus, in its most general form, the host–parasite coevolution hypothesis seems to be simultaneously an instance of both of Felsenstein's categories.

COSTS OF SEX AND RECOMBINATION

The problem of sex and the problem of recombination are closely related, but they are not simply two names for the same thing. Given that a population reproduces sexually, there still remains the vexing question as to why its recombination rates do not evolve downward toward zero (e.g., Nei, 1967; Feldman, 1972; Feldman and Libermann, 1986; Felsenstein, in this volume), and more generally, there remains the question as to why its recombination rates should have equilibrium values other than zero and one-half (e.g., Charlesworth, 1976; Hutson and Law, 1981; Brooks and Marks, 1986; Brooks, in this volume). But the conditions that favor recombination, given sex, may be much less stringent than those that favor sex itself, given fully viable asexual mutants (e.g., Maynard Smith, 1978).

Under outcrossing, half of a population's parental investment will go into males (or, more generally, male reproductive functions). If males do not themselves rear offspring, then an asexual form that produced entirely female progenies would have a rate of increase that was twice that of its sexual counterparts, and it would drive them to extinction in very few generations (Maynard Smith, 1971). This is the twofold cost of sex. It is sometimes referred to as the cost of meiosis, but it is less a consequence of meiosis than it is of the sex ratio, in species where only the females rear offspring. If males contribute as much as females do to the rearing of offspring, then there is no cost of sex in this ecological sense, because an all-female asexual clone would have no reproductive advantage over an equivalent sexual species. Nonetheless, a new parthenogenic mutation arising within the sexual species could increase, *if* the sexual males unwittingly paired with the parthenogenic females and helped to rear their offspring. But as this mutation increased in frequency, the number of available males would decrease, and in the end there would be a new all-female clone with no reproductive advantage over an equivalent sexual species whose males mated only with their sexual conspecifics (e.g., Uyenoyama 1984). Selfing reduces the cost of sex by permitting the evolution of strongly female-biased patterns of reproductive allocation, but it also reduces the potential benefit of recombination by creating extensive homozygosity. In many respects, partial selfing can be viewed as a continuously adjustable approach to asexuality.

It is sometimes argued that obligately outcrossed species lack the genetic variation that would easily allow them to give up sex, and that except for this constraint, many would do so. This presumed inability to experiment with asexuality is often viewed as a product of group or species selection, on the assumption that sex may permit the long-term survival of a population, despite its short-term disadvantages. But many species of cyclically or facultatively parthenogenic animals (and self-compatible plants) could easily go literally (or effectively) asexual, if selection were pushing them in that direction (Williams, 1975; Maynard Smith, 1978). It follows that outcrossed sexuality, with its attendant sex-ratio penalty, must somehow be paying its own way in these species, and that a satisfying *general* explanation for the prevalence of outcrossed sex should not appeal to long-term group or species selection, but should instead identify short-term benefits of sexual reproduction that give it something like a compensating twofold advantage over asex.

Nonetheless, strong developmental barriers against an easy switch to asexuality could exist in some taxa, and these barriers could have evolved through group selection. A sexual lineage that easily gave rise to viable asexual forms might often find itself driven to local extinction through competition with its own asexual derivatives. If the evolutionary inflexibility of the conquering asexual forms in turn doomed *them* to early extinction, then the lineage might not leave many descendants, compared to an equivalent lineage in which there happened to be no developmentally feasible route to asexuality. But the fact that asex and selfing *are* viable alternatives in some taxa shows that short-term

advantages to sex must exist, at least in those taxa. And there is no reason to suppose that such advantages exist *only* in taxa showing lapses from exclusively outcrossed sexuality. Thus even if we knew that group-selected barriers to asex had evolved in some taxa, the problem of the twofold cost would still be with us.

These arguments are well known, and they are discussed in several other chapters in this volume. We have rehearsed them here to emphasize that a full explanation for sex requires that it often have large and persistent selective advantages over asex. The attraction of parasites is that they seem likely to be able to generate such advantages.

PARASITES AND POLYMORPHISM

There can be no benefit in reducing linkage disequilibrium unless ecologically significant genetic polymorphism actually exists. Thus we need to ask first, whether host–parasite interactions are expected to cause the accumulation of such polymorphism, and second, whether there is evidence that they do so.

Theory

Host–parasite coevolution can be viewed metaphorically as an "arms race," in which each side is continually searching for new and improved methods of defense or attack. If the new methods are unconditionally better or worse than the existing methods, then the mutations giving rise to them will either sweep to fixation or be lost, and there will be no tendency to accumulate polymorphism. But if better methods of defense or attack tend to *cost* more than their alternatives (in that they drain resources away from reproduction), then a "better" defense will be of net benefit to a typical host individual *only* if the host is likely to be attacked by a parasite against which no weaker (and cheaper) defense will work. The parasite faces a similar dilemma, and thus the two species find themselves playing an evolutionary game that is closely related to the well-known "war of attrition" (Maynard Smith, 1974, 1982). Similarly, if the differences among phenotypes are *qualitative*, such that particular defenses simply work best against particular attacks, and vice versa, with no differences of intrinsic cost, then host and parasite can be viewed as a pair of coupled multiple-niche models, in which each species provides a variable environment for the other. In either case, the relative fitness of a given defense (or attack) will depend on the frequencies of the different attacks (or defenses) currently being employed by the other species.

Under these circumstances a polymorphic equilibrium may exist (e.g., Mode, 1958; Gillespie, 1975), but if the full genetic and population dynamics of both species are included in the model, the equilibrium is likely to be unstable (e.g., Person, 1966; Jayakar, 1970; Yu, 1972; Clarke, 1976; Rocklin and Oster, 1976; Auslander et al., 1978; Lewis, 1981a,b; Anderson and May,

1982; May and Anderson, 1983a,b; Eshel and Akin, 1983; Levin, 1983; May, 1985; Bell and Maynard Smith, 1987; see also Maynard Smith and Brown, 1986). The boundaries are usually unstable as well, which implies that the two species will engage in some kind of permanently dynamical "chase" through the gene-frequency and population-size planes. As one host genotype increases in frequency it favors the increase of the parasite genotype best able to exploit it, whose subsequent increase lowers the fitness of that host genotype, allowing a different host genotype to increase, which favors a different parasite genotype, and so on.

Levin (1975) applies Whittaker's (1969) famous coevolutionary metaphor to the special case of host and parasite, who sweep back and forth across the evolutionary "dance floor." This captures the sense of lively, coupled movement, and almost makes it sound like fun. But do the partners spend most of their time out in the middle of the floor? Or do they tend to bump into the walls? In particular, do the dynamics tend to keep the *host* species polymorphic? If not, then the host will usually have little to gain from recombination.

In the simplest one-locus models without mutation or migration, the two species either circle endlessly in a neutrally stable orbit determined by the initial conditions (if the model is cast in continuous time), or else they spiral outward toward the boundaries (if the model is cast in discrete time). Figure 1 illustrates the dynamics of one such model. In most models of this kind, as in this one, the fitnesses of the host genotypes depend only on the current frequencies of the parasite genotypes, and vice versa. But the current state of the parasite population reflects the recent history of the host, so the fitnesses of the host genotypes depend, indirectly, on their *own* frequencies over many *previous* generations. The same is true of the fitnesses of the parasite genotypes. Thus any genotype that was common in the recent past is likely to suffer relatively low fitness at present, because of the evolutionary change that its commonness induced in the other species. In effect, the current position of each species is a "memory" of the recent history of the other, and so the fitnesses of the genotypes within each species appear to exhibit negative frequency dependence with a time delay, even though there is no *explicit* intraspecific frequency dependence in the model.

In general, there are no stable internal equilibria in models of this kind unless they incorporate some form of explicit intraspecific frequency dependence, density dependence, or heterozygote advantage. Thus in a finite world, their cyclical dynamics would be likely to degenerate into irregularly spaced episodes of monomorphism, punctuated first in one species, then in the other, by the reintroduction of the lost allele and its rapid passage to fixation. This would not seem to be very favorable for sex, since any given locus would tend to be monomorphic for long periods of time. But there are several ways to rescue the situation.

First, there is the appeal to mutation and migration. The tendency to spiral outward can be arrested even in the simplest discrete-time models by remarkably

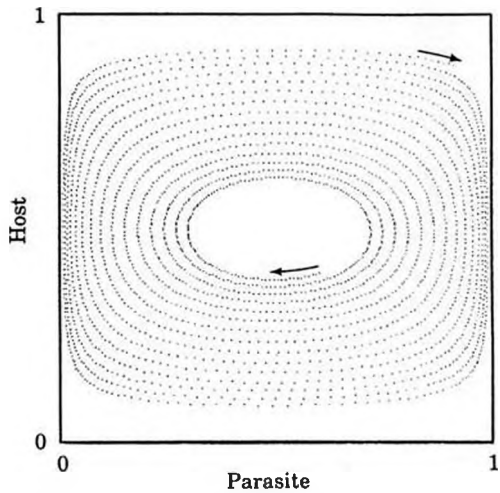

FIGURE 1. Gene-frequency trajectory of a simple 1-locus host-parasite model. Each species has a single haploid locus with two alleles, at frequencies h_1 and $h_2 = 1 - h_1$ in the host and p_1 and $p_2 = 1 - p_1$ in the parasite. Hosts and parasites encounter each other at random, so the probability that any given host individual is attacked by parasite type 1 is proportional to p_1. Parasite type 1 is most successful on host type 1, and parasite type 2 is most successful on host type 2, while hosts are most successful against parasites of opposite type. Thus the expected fitness of a type 1 host is negatively proportional to the frequency of type 1 parasites: $W(\textit{host } 1) = (1 - s)p_1 + p_2$, where s is the penalty, to the host, caused by successful parasitism. Conversely, the expected fitness of a type 1 parasite is positively proportional to the frequency of type 1 hosts : $W(\textit{parasite } 1) = h_1 + (1 - t)h_2$, where t is the penalty, to the parasite, caused by the host's successful defense. The fitnesses of type 2 hosts and parasites are constructed in exactly the same way. Given these four fitnesses, it is easy to write down the recurrence equations for h_1 and p_1. For $0 < s < 1$ and $0 < t < 1$, the central equilibrium at (0.5, 0.5) is unstable, as are the boundaries. The case illustrated here is $s = 0.05$, $t = 0.15$. Each point shows the gene frequencies of parasite and host (p_1, h_1) in one generation, and the entire trajectory is 2500 generations long.

small inputs of genetic variation uncorrelated with the current state of the population (Figure 2). A low rate of mutation or migration gives rise to a stable limit cycle near the boundaries, and as the rate is increased the cycle shrinks inward toward the central equilibrium point, which is finally stabilized at rates above a certain critical value (see legend to Figure 2).

Second, there is the appeal to multiple alleles. The two-allele model of Figures 1 and 2 always cycles in a highly stereotyped and regular way, but the equivalent three-allele model has very complex dynamics that depend more strongly on parameter values and initial conditions than do those of the two-allele models (Figure 3). Without mutation or migration, the three-allele gene-frequency trajectories eventually become stuck near the boundaries, as in the

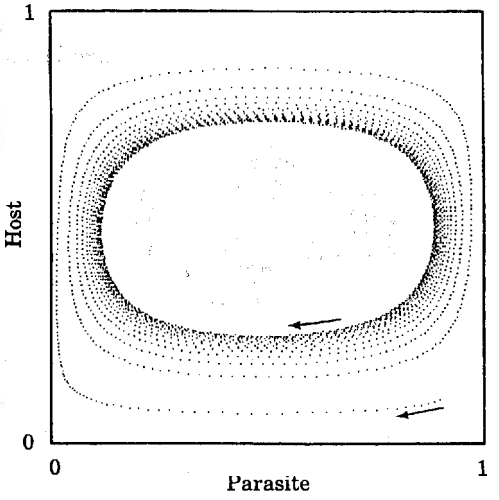

FIGURE 2. Gene-frequency trajectory of a simple 1-locus host-parasite model with mutation in the parasite. This model is exactly the same as the one described in the legend to Figure 1, except that the parasite species experiences a mutation rate m (which can also be thought of as a migration rate). If the mutation rate exceeds $0.25st/(2 - s - t + st)$, then the central equilibrium at (0.5, 0.5) becomes stable. Lower mutation rates give rise to stable limit cycles, such as the one illustrated here for $s = 0.05$, $t = 0.15$, $m = 0.0005$. As in Figure 1, the points show the joint gene frequencies of parasite and host in successive generations, and the total length of the trajectory is 2500 generations.

two-allele model, but the time to quasifixation may be longer than in the two-allele case. This suggests that the relatively chaotic dynamics of a highly multiallelic system might be less inclined to drive particular alleles to very low frequencies than are the more regular dynamics of a system in which there are only two possible allelic states in host and parasite.

Third, there is the appeal to multiple loci. The argument here is that although most loci may be monomorphic most of the time, enough of them will be polymorphic enough of the time to give an advantage to recombination. In effect, this is the Fisher–Muller view of multilocus evolution: A favorable new mutation is almost guaranteed to be out of linkage equilibrium with alleles at other loci, and this may retard its progress to fixation. The argument applies to every kind of transient polymorphism, no matter what its cause, so parasites retain a special importance only to the extent that they are a frequent cause of adaptive gene substitutions (Hamilton, 1986).

Finally, there is the appeal to biological complexities not represented in the simplest models. These range from molecular and physiological details of the way in which host and parasite interact (e.g., mechanisms of acquired immunity), through their life history patterns (e.g., parasite life cycles involving more than one host species), to their population structures (e.g., subdivided host

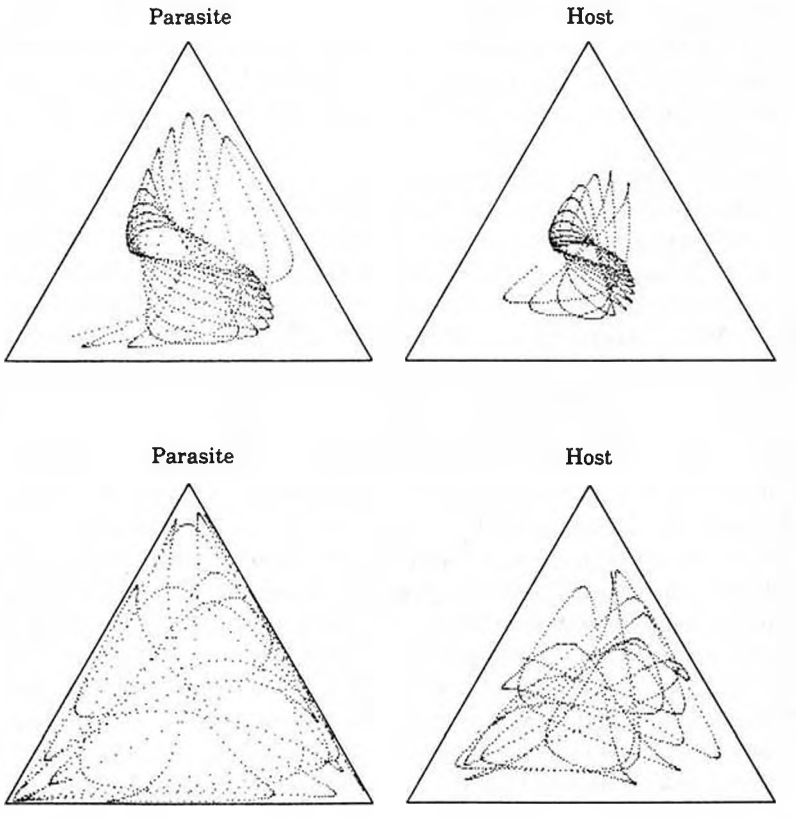

FIGURE 3. Gene-frequency trajectories of a simple 3-allele host-parasite model. The model illustrated here is the 3-allele generalization of the model described in the legend to Figure 1. Each of the three parasite genotypes successfully attacks one of the three host genotypes, and suffers a fitness penalty t when associated with either of the other two host types. Likewise, each host suffers a fitness penalty s when successfully attacked by the one parasite type that can penetrate its defenses. There is no mutation in the model shown here, although mutation in the parasite has essentially the same kind of stabilizing effect in the 3-allele case as it does in the 2-allele case shown in Figure 2. Separate gene-frequency trajectories for parasite and host are shown here, since a phase diagram can only show the frequency of one allele in each species. The fitness parameters s and t have the same values as in Figures 1 and 2, and the trajectories are again 2500 generations long (but here *every other* generation is plotted, rather than every one). The upper pair of trajectories begin at a point chosen to be similar to the starting point of Figure 1; the lower pair are the continuation of the trajectory shown in the upper pair. Thus 5000 generations are shown in all. All meaningful values of s and t and all starting points apparently lead eventually to chaotic gene-frequency dynamics, in the absence of mutation or migration. Both species may eventually become stuck near the boundaries most of the time, but each continues to make at least occasional passsages out through the middle of its gene-frequency space.

populations with limited migration among subdivisions). In many of the cases studied to date, the addition of realistic detail has reduced either the occurrence or the severity of cycling (e.g., May and Anderson, 1983a,b; Bremermann and Fiedler, 1985), but in some cases it has increased the tendency to cycle (e.g., May, 1985).

One very important detail is the generation time of the parasite (Anderson and May, 1982). If this is much shorter than that of the host (as is often the case), then the parasite population may more or less fully adapt, within each *host* generation, to the current distribution of host genotypes. In the limit, each host generation faces an array of parasite attack strategies that depends only on the distribution of genotypes in the *previous* generation of hosts. This greatly shortens the effective time delay in the frequency dependence experienced by host genotypes, and thereby gives rise to shorter cycles more likely to produce sustained polymorphism at loci controlling the host's defenses. Indeed, under various kinds of simplifying assumptions it all but eliminates the need even to model the actual dynamics of the parasite population, which can be represented as a simple phenomenological frequency dependence of the genotypic fitnesses of the host population, perhaps with a short time delay. This is the route taken by many "host–parasite" models, especially those that focus on the possible advantages of sex and recombination in the host (e.g., Hamilton, 1980, 1982; Hamilton et al., 1981; Hutson and Law, 1981; May and Anderson, 1983a,b; May, 1985). In some models this process of abstraction is carried even farther, and the parasite population is represented as a regime of *externally* imposed alternating fitness differences among the various host genotypes (e.g., Eshel and Hamilton, 1984; Kirkpatrick, 1985).

Hamilton (1980, 1982) and Hamilton et al. (1981) explore one-locus diploid and two-locus haploid models with phenomenological negative frequency dependences of the form

$$W_i = \exp[d(1 - xp_i)]$$

where d is a parameter that sets the strength of the frequency dependence, x is the number of different genotypes (two or four), and p_i is the frequency of genotype i, either in the present generation or in the previous one. May and Anderson (1983b) examine similar models in which the fitnesses are derived from standard epidemiological models for infectious microparasites such as viruses and bacteria. Parameter values corresponding to mild frequency dependence tend to give stable polymorphic equilibria, but more extreme values give rise to two-point cycles and, in some cases, to higher-order cycles and finally chaos (see also May, 1985).

In the two-locus haploid models, these cycles may involve alternating coefficients of linkage disequilibrium, where an excess of coupling gametes (*AB* and *ab*) in one generation is followed by an excess of repulsion gametes (*Ab* and *aB*) in the next, without any gene-frequency changes at all! Here the advantage of recombination is easy to see, since it allows the common (favored) genotypes

in one generation to produce, among their progeny, reasonably large numbers of the rare (disfavored) genotypes that *will* be favored in the next. As a result, the geometric mean fitness of a sexual population can be much larger than that of the corresponding asexual population. In effect, the sexual population "hedges its bets" by *retarding* the rate at which its *genotype* frequencies respond to selection. These models are extremely artificial, but they show that intense frequency dependence can generate temporally varying linkage disequilibria of the kind that may strongly and persistently favor recombination (Charlesworth, 1976; Hutson and Law, 1981; see also Bell and Maynard Smith, 1987).

But if the frequency dependence is not so extreme, so that the host's genotype frequencies cycle only weakly or not at all, then recombination may actually be selected against. To see why, consider again the two-locus haploid model with four genotypes (*AB*, *Ab*, *aB*, and *ab*) and suppose that the fitnesses of these genotypes are identically frequency dependent according to a scheme such as the one mentioned above, so that there is a stable polymorphic equilibrium with all four genotypes present in equal frequencies. Then there will be no linkage disequilibrium and no advantage (or disadvantage) to recombination. But if the pattern of frequency dependence is made less symmetrical, so that the equilibrium genotype frequencies are *not* in linkage equilibrium, then recombination will tend to generate too many of the genotypes with the lower equilibrium frequencies, and modifiers of recombination that tighten linkage will tend to be favored by selection (e.g., Feldman and Libermann, 1986; Felsenstein, in this volume). Indeed, a mixture of four asexual clones would easily keep itself at the equilibrium frequencies, and given the sex ratio advantage discussed above, such a mixture would overwhelm even a nonrecombining sexual population.

In all of the models discussed so far, the negative frequency dependence of fitnesses is caused by the presumed complementary specificity of the interactions between hosts and parasites. From the point of view of an individual host, it is bad to be common because the parasites best able to evade your defenses are themselves likely to be common. With two alleles at each of two loci, no genotype can remain rare for long. We need to ask whether any qualitatively new behavior is likely to arise in more complex models that permit real rarity, which is to say, in models with many alleles at each of many loci.

Given an overall pattern of negatively frequency-dependent genotypic fitnesses and a very large population size, it is clear that (1) many alleles could be maintained at each locus, and (2) a system that involved several loci in the determination of the host's defensive phenotype might have great advantages over a system that involved only one or two loci. Under these assumptions the number of functionally distinct host genotypes might be very large. In an infinite world this would make no difference; a cloud of clones, each at low frequency, would still defeat an equivalent sexual species, as long as the dynamics of interaction between host and parasite did not give rise to vigorous cycling. But in a finite world there are limits to the number of genotypes that can be

maintained, even in the absence of cycling, in either a sexual or an asexual population. In particular, rare asexual clones are always at risk of going extinct (Treisman, 1976). Rare sexual genotypes may also disappear, of course, but if their constituent alleles remain in the population, then they can be recreated in subsequent generations. As is often remarked, only in a sexual population can every individual be unique. With respect to defense against parasites there may be no particular advantage in being unique, but there may be great benefit in being very rare.

Will a recombining sexual population actually maintain the multilocus allelic diversity required to give it an average genotypic diversity greater than that maintained by an equivalent asexual population of the same finite size? Intuition suggests that it should, but many intuitively reasonable arguments about recombination have turned out to be wrong. Here one might also imagine that in a system with many loci, each individual locus is so unimportant that it could easily slide into monomorphism if unconstrained by linkage to other, functionally related loci (e.g., Lewontin, 1964b, 1980; Franklin and Lewontin, 1970). To explore this question we constructed the simplest possible Monte Carlo simulation of a finite population subject to frequency-dependent selection with respect to an eight-locus, two-allele haploid genotype. Each of the 256 possible genotypes is assumed to determine a unique phenotype, with a fitness inversely proportional to its frequency. For a wide range of population sizes, rates of mutation or migration, and strengths of selection, more genotypic diversity is maintained under sexual than under asexual reproduction, and this is reflected in higher average fitnesses of the sexual populations. The disparity in genotypic diversity (and hence average fitness) between sexual and asexual reproduction becomes very large for population sizes on the order of 100. Some typical results are shown in Table 1, with the model described more fully in the legend.

In summary, the dynamics of host–parasite interaction tend to give an advantage to rare host genotypes, under the usual assumption that coevolution between host and parasite tends to produce complementary attack and defense phenotypes. But this advantage of rarity may or may not cause large amounts of variation to accumulate in the host, depending on many details of the life histories, population structures, and genetic systems of both species. The relative generation time of the parasite, its mode of transmission, its average virulence, and its effect on the population density of the host have all been identified as important variables, as has the host's ability to mount immune reactions. But polymorphism can apparently be maintained if there is some degree of complementarity between the genotypes of host and parasite, and if there exist one or more complicating factors sufficient to prevent runaway cycling of the kind that leads to effective monomorphism.

Before looking more closely at the ways in which parasite-induced polymorphisms might give an advantage to sexual reproduction, we will briefly

TABLE 1. Equilibrium genotypic diversities and average fitnesses in an eight-locus simulation of frequency-dependent selection[a]

N	m	Reproductive System	Average Number of Genotypes	Average Genotypic Diversity	Average Fitness
1024	10^{-3}	sex	222	131	0.99
		asex	68	34	0.97
	10^{-5}	sex	201	108	0.99
		asex	18	16	0.94
256	10^{-3}	sex	96	56	0.98
		asex	21	13	0.92
	10^{-5}	sex	60	37	0.97
		asex	8	7	0.86
64	10^{-3}	sex	25	15	0.93
		asex	8	6	0.82
	10^{-5}	sex	8	7	0.85
		asex	3	3	0.66

[a]The model species is either hermaphroditic or asexual. There are 256 possible genotypes (eight haploid loci, each with two alleles). The fitness of each genotype is $W_i = 1 - p_i$. The distribution of progeny sizes is Poisson. N is the total population size, and m (or migration) is the mutation rate per locus per generation. Each set of conditions was run to approximate equilibrium (1000 generations), and then the number of genotypes present, the genotypic diversity, and the mean fitness was calculated every 20 generations, for the next 200. Each number given in the table is the average of these 11 figures, averaged again over four independent runs. Genotypic diversity is calculated as $1/\Sigma p^2$. Results were highly consistent within and between runs.

mention (without attempting to review) the various lines of evidence indicating that such polymorphisms exist.

Evidence

Complementary "gene-for-gene" systems appear to be fairly common in certain crop plants and their fungal pathogens (e.g., Flor, 1956; see Day, 1974; Barrett, 1983, 1985; Bell, 1985; Bremermann 1985). These systems motivate most of the fully coevolutionary models that have been published to date. Barrett (1985) argues that these systems are usually more complicated and less symmetrical than is commonly believed and that the equivalent systems in undomesticated species are even messier. Thus a one-to-one relationship between genes in the host and genes in the parasite is an extreme instance of relationships that are

probably more often one-to-many, many-to-one, or even many-to-many (i.e., fully polygenic on both sides). But even though the genetics of these systems are usually more complicated than the simple gene-for-gene hypothesis would suggest, phenotypes still tend to exhibit complementary specificity.

Variation in innate resistance to protozoans and helminths has been documented for several animal species, especially mice (see Hamilton, 1982; May and Anderson, 1983a,b; Holmes, 1983; Blackwell, 1985; Wakelin, 1985a,b; Wassom, 1985; Sher et al., 1986), but in only a few animal systems is there yet any evidence for the complementarity that motivates the models discussed above (e.g., Benjamin and Briles, 1985). Several genetic complexes assumed on functional grounds to affect disease resistance are notoriously polymorphic (e.g., HLA in human beings), and there is epidemiological and other genetic evidence that different genotypes may vary in their susceptibility to different diseases (for entries to the literature on HLA, see Ryder et al., 1981; Thomson, 1981; Bodmer, 1986a,b; Hedrick et al., 1986). But showing that a system is polymorphic, or even that there is variation for resistance, is not the same as showing that the polymorphism is maintained by frequency-dependent interactions with particular species of parasites (Levin et al., 1982). It may be difficult to imagine what *else* could be maintaining all that polymorphism, but as yet there seems to be little direct evidence, even of the limited sort that exists for crop plants and their fungal pathogens.

At the phenotypic level there is abundant evidence of negative frequency dependence, mainly from experiments on grasses (e.g., Allard and Adams, 1969; Antonovics and Ellstrand, 1984; see Bell, 1985). Although these experiments show clearly that individuals may be fitter when surrounded by unrelated nearest neighbors than when surrounded by close relatives, for the most part they say nothing about the mechanisms generating the frequency dependence. There are, however, a few experiments showing that mixtures of inbred lines may suffer less damage from pathogens than do monocultures (Barrett, 1981), and suggesting that this may be one reason for their superior yields (Wolfe and Barrett, 1980; Wolfe et al., 1981).

Many patterns in the geographical distribution of plant breeding systems and animal parthenogenesis conform to the general expectation that sex and recombination should be most valuable in stable, biotically rich environments, and least valuable in physically harsh, disturbed, or otherwise biotically impoverished environments (e.g., Ghiselin, 1974; Levin, 1975; Glesener and Tilman, 1978; Maynard Smith, 1978; Bell, 1982, 1985; but see Lynch, 1984, for a critique). This association is consistent with the view that parasites are most troublesome in biotically rich environments (e.g., in the tropics), but it is also consistent with the view that sex is an adaptation to straightforward competitive and prey–predator interactions.

Annual plants are more often self-pollinating or apomictic than are perennials (Levin, 1975). This is consistent with the idea that perennials should be more troubled by parasites than should annuals, because they are easier to find

and have longer generation times. But perennials should also be more troubled by competitors, so again the comparative evidence tends to be ambiguous.

The strongest evidence of complementary coadaptation between hosts and parasites in nature comes from the work of Edmunds and Alstad (1978, 1981) on the black pine leaf scale, a homopteran that infests Douglas fir and several species of pines in western North America. Scales show limited dispersal, and they are completely sedentary once settled on a host. Adjacent trees often differ enormously in their total load of scales, but most trees become more seriously infested as they grow older. Through a series of reciprocal transplantation experiments, Edmunds and Alstad have shown that the increased infestation of older trees is explained mainly by the local adaptation of their indigenous populations of scales, and not by a general weakening of defenses with age.

Scales are haplodiploid (males are haploid, and females diploid). Alstad and Edmunds (1983) show that where two adjacent trees touch each other, the sex ratio tends to be lower than it is on the opposite sides of the same trees. Alstad and Edmunds interpret this as evidence of "outbreeding depression" caused by gene flow between the two populations of scales, each of which is better adapted to its own host than to the other; males, being haploid, are expected to suffer worse from the effect than are females. Pines and firs defend themselves with extremely complex and individually variable mixtures of terpenes and other toxic compounds (e.g., Sturgeon, 1979), so it is possible that scales benefit by adjusting their own defenses to the particular mixtures produced by their host trees. In principle, this hypothesis could be tested experimentally.

On balance, the existing evidence is favorable to the idea that parasites are often a cause of polymorphism at loci controlling certain aspects of the defenses of their hosts, but it is not yet decisive as to the generality or the importance of the phenomenon. The main problem is that different kinds of evidence tend to come from different systems—genetics here, population biology there, physiology somewhere else. When the chain of causation has been tied together at all these levels for even one system, the fragmentary evidence from other systems will probably seem more coherent, and thus more compelling, than it does at present.

POLYMORPHISM AND SEX

Given polymorphism, there remains the question as to how it favors sex and recombination. As Felsenstein (1985, and in this volume) has emphasized, recombination accomplishes only one thing: the reduction of linkage disequilibrium. If this is to be advantageous, then there must be epistatic fitness interactions between loci whose linkage disequilibria periodically change sign, either because of drift or because of changing patterns of selection.

Complementary attack and defense interactions of parasites and hosts could generate epistasis on the fitness scale, but we are not aware that this has ever been demonstrated, even in the well-studied gene-for-gene systems. To the

extent that rarity per se is favored, epistasis is almost guaranteed, since particular combinations of alleles may be very rare even if each of the constituent alleles is itself fairly common. This would seem to be, at least in principle, a special strength of the host–parasite hypothesis.

Fluctuating disequilibria can easily be generated by random drift, giving rise to the "Fisher–Muller" version of host–parasite coevolution, as exemplified by the simple model discussed earlier and illustrated in Table 1. Because host–parasite models have an innate tendency to cycle, the perturbations caused by sampling in finite populations may also set off spiraling gene-frequency changes that generate additional, selectively induced linkage disequilibria, even where the interactions are not of a form that would sustain such cycles in the absence of stochastic perturbations (Figure 2). These selectively induced linkage disequilibria would also change over time, depending on the phase of the cycle at which the population found itself, propelled by a combination of random and deterministic forces. No such effects are seen in the stochastic model described above and illustrated in Table 1, because the parasite population is represented implicitly by a simple fixed pattern of negatively frequency-dependent genotypic fitnesses in the host. A finite-population model with evolving parasites would be very difficult to analyze, but might prove interesting. In any event, such a model would apparently be one in which randomly induced and selectively induced linkage disequilibria were inseparably entwined; it would therefore be simultaneously a Fisher–Muller model *and* a Sturtevant–Mather model, in Felsenstein's taxonomy.

In an infinite population governed entirely by deterministic dynamics, cycles giving rise to changing linkage disequilibria can also be sustained, as emphasized by Hamilton (1980, 1982, 1986), but the interactions between host and parasite need to be stronger than they do in the case of a finite population. Extreme parameter values are needed to generate two-fold fitness advantages for sexual reproduction in the simple two-locus models studied to date, but more complicated multilocus or multiallele models are likely to produce large advantages for sex under reasonable assumptions about the fitness differences associated with different host genotypes (May and Anderson, 1983b; Weinshall, 1986). In principle, several independent mechanisms, each of which produced a small advantage for sex and recombination, could be combined to produce a cumulative advantage of almost any desired size. This argument applies to all kinds of mechanisms, not just those defending hosts against parasites. But the members of a typical species probably face parasitic threats from several quarters, and the defenses involved seem likely to be at least partly distinct from each other.

Where sex involves active mate choice it can do more than reduce linkage disequilibria. In theory it can actually *generate* linkage disequilibria, but more plausibly, it can change gene frequencies. If hosts and parasites are engaged in coevolutionary gene frequency cycles of intermediate length and severity, then much of the time there is likely to be heritable variation for fitness within the

host population (Eshel and Hamilton, 1984). Hamilton (1980, 1982) has argued that under these circumstances, females in polygynous species might benefit from attempting to choose mates that were relatively free of parasites, and thus relatively likely to have genotypes conferring above-average resistance to the currently dominant strains of parasites. Kirkpatrick (1985) describes a three-locus model in which female choice for a "showy" male trait that reveals parasite burdens can be driven to fixation, under an externally imposed regime of alternating selection at the locus controlling resistance. Such a pattern of female choice might pay part of the cost of sex in polygynous species (which tend to suffer the full twofold cost because they typically have no male parental investment), but it is not clear how large the benefit might actually be, since the best resistance genotypes are being favored by natural selection anyway.

Regardless of the extent to which female choice could help to pay the cost of sex, it provides an opportunity to test specific hypotheses that arise as implications of the more general hypothesis that host–parasite interactions generate heritable fitness differences. For example, Hamilton and Zuk (1982) and Read (1987) show that brightly colored bird species tend to carry more genera of blood parasites than do duller species, as might be expected if sexual selection tends to be relatively strong in species that are relatively prone to infection. Like most comparative studies, this one cannot rule out alternative schemes of causation, but these can be examined experimentally, and several such experiments are now under way or soon to be reported (e.g., Zuk, in press; J. A. Endler, personal communication).

SUMMARY

Selectively important linkage disequilibria involving loci that affect the interactions between hosts and parasites could be caused either by selection or by drift (or both), and they could vary either in time or in space (or both). Thus parasites, as agents of selection, are not tied even in principle to any particular category of models for the evolution of sex and recombination. As Bell (1985) points out, they could play as important a role in Tangled Bank models (which emphasize spatial variation) as they do in Red Queen models (which emphasize temporal variation). The asymmetry would appear to lie in the greater dependence of Red Queen models on a role for parasites, since it is difficult to imagine what other selective agency could provide sufficiently large and rapidly changing fitness differences, involving epistatically interacting loci.

There remain many interesting theoretical issues to be explored, particularly those involving realistic details of host and parasite life histories (both of which can be very complicated), in the context of fully coevolutionary treatments of the dynamics of both species or, even better, *several* species of hosts and parasites (see Hamilton, 1986). These models will be frighteningly complex. Artful simplifications will undoubtedly be the key to making their behavior understandable.

But the main need, as we see it, is for more evidence concerning the actual interactions between hosts and parasites, at both the individual and the population levels. In particular, it seems important to know much more than we do about the costs of various attack and defense mechanisms, ideally for both members of a pair of interacting species (but see Levin and Lenski, 1983, 1985, for bacteria and viruses), and it also seems important to know how far we can generalize from the complementary genetic systems of plants and their fungal parasites (Barrett, 1985). Without such evidence there are too few constraints on models intended to answer questions about the amounts of ecologically significant polymorphism that might be maintained by host–parasite interactions. Many of the relevant experiments are ecological and evolutionary in scope, so they will require large population sizes and large numbers of generations. Levin et al. (1982) consider the kinds of experimental systems that are most likely to prove both tractable and useful for these purposes.

By contrast, there seem to be few limits (other than imagination and knowledge of natural history) on the number of potentially testable comparative predictions that could be generated from the basic premise that host and parasite may be engaged in a fast-moving coevolutionary struggle. For example, if infections tend to spread in epidemic fashion within large social insect colonies, then we might expect social species to engage more frequently in multiple mating, and to have higher rates of recombination, than do their solitary relatives (Tooby, 1982; Hamilton, 1987; Sherman et al., in press). For similar reasons, butterfly species that live at low population densities might be expected, other things being equal, to distribute their eggs singly or in small groups among a large number of host plants, rather than piling them together on a few plants, where there is greater risk that an epidemic could take hold among a large group of relatively homozygous and genetically similar siblings. We expect that many interesting new predictions will soon be made concerning the ecological and demographic correlates of mating systems in various groups of plants and animals. Comparative studies will not address the quantitative questions that arise from the abstract theory, but they may nonetheless derive a great deal of power from the way they exploit distinctive features of the biologies of particular groups of organisms.

After this was written, Burt and Bell (1987) reported that excess chiasma frequency in the males of 24 species of undomesticated mammals is positively correlated with age of sexual maturity. Excess chiasma frequency is defined as the total number of chiasmata in excess of one per bivalent. The raw correlation is very strong ($r = 0.88$), as is the partial correlation taking out the effect of body size ($r = 0.69$). Neither excess chiasma frequency nor age of maturity is correlated with chromosome number, and excess chiasma frequency is negatively correlated with litter size. Burt and Bell interpret this pattern as evidence "that crossing-over may function to combat antagonists with short generation times but does not function to reduce sib competition."

This hypothesis is similar in spirit to the one mentioned above, concerning the recombination rates of social insects and their solitary relatives, with life span in mammals playing the role of colony size in insects. In each case, the factor expected to promote recombination is one that is expected to make the species a relatively easy target for fast-evolving pathogens. Social insects appear to have higher chromosome numbers than their solitary relatives (Sherman 1979, Seger 1983), but Burt and Bell (1987) find no evidence that chromosome number is related to age at maturity in mammals. It will be interesting to see whether this apparent inconsistency between the two groups of organisms can eventually be resolved, and whether similar patterns can be found in other groups.