Imperfect Genes, Fisherian Mutation and the Evolution of Sex

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ABSTRACT

In this paper we present a mathematical model of mutation and selection that allows for the coexistence of multiple alleles at a locus with very small selective differences between alleles. The model also allows for the determination of fitness by multiple loci. Models of this sort are biologically plausible. However, some previous attempts to construct similar models have assumed that all mutations produce a decrease in fitness, and this has led to a tendency for the average fitness of population members to decline when population numbers are finite. In our model we incorporate some of the ideas of R. A. FISHER, so that both deleterious and beneficial mutations are possible. As a result, average fitness tends to approach a stationary distribution. We have used computer simulation methods to apply the Fisherian mutation model to the problem of the evolution of sex and recombination. The results suggest that sex and recombination can provide very large benefits in terms of average fitness. The results also suggest that obligately sexual species will win ecological competitions with species that produce a substantial fraction of their offspring asexually, so long as the number of sites under selection within the genomes of the competing species is not too small and the population sizes are not too large. Our model focuses on fertility selection in an hermaphroditic plant. However, the results are likely to generalize to a wide variety of other situations as well.

WHY do so many species produce their offspring by means of sexual reproduction? One possible answer to this question is that sex evolves and is maintained because it enhances the fitness of members of lineages in which sexual reproduction has been practiced. This sort of "adaptationist" hypothesis about the evolution of sex is the most common one pursued in the scientific literature (MICHOD and LEVIN 1988; HURST and PECK 1996), although there have been alternative approaches (*e.g.*, ROSE 1983).

If an adaptationist answer to the question of sex is correct, then the sexual mode of reproduction must fulfil at least three requirements. First, it must not inevitably lead to the rapid demise of species through, for example, the spreading of contagious diseases. Second, populations in which some offspring are produced sexually must not inevitably be susceptible to the spread of mutations that enhance the rate of asexual reproduction. Finally, sex must not produce a strong disadvantage in between-species competitions for resources. Most theoretical work on the evolution of sex has focused on the last of these three requirements (either explicitly or implicitly). In this paper we follow this tradition. However, we believe that our results have bearing on satisfaction of the first two requirements as well.

On the face of it, the ability of sexual species to survive despite competition from more-or-less asexual competitors seems surprising. To see why, consider the case of an outcrossing hermaphroditic plant in which resources available for reproduction can be devoted either to the production of seeds or to the production of pollen. Say that the number of seeds that an individual can produce is proportional to the amount of resources devoted to seed production, and likewise for pollen production. Under these conditions, application of R. A. FISHER's ideas about sex allocation lead to the conclusion that, at equilibrium, half of each individual's reproductive resources will go into seed production and half into pollen production (FISHER 1930; CHARLESWORTH and CHARLESWORTH 1981).

Now, consider a second species that competes for the same resources as the sexual species and that is also characterized by the same sort of trade off between pollen production and seed production. Say that, in this second species, a proportion ϕ of the seeds are produced sexually, and the rest are produced asexually. Thus, the sexual species mentioned above would be characterized by $\phi = 1$, and an entirely asexual species would be characterized by $\phi = 0$. Application of CHARLESWORTH and CHARLESWORTH's analysis (1981) shows that, in such a species, we can expect that the equilibrium proportion of resources that will be devoted to seed production is $[1 - (\phi/2)]$. This means that, all else being equal, per-capita seed production will decrease linearly as ϕ increases, and an obligately asexual species ($\phi = 0$) will produce twice as many seeds as an obligately sexual species ($\phi = 1$). This observation embodies the so-called twofold cost of sex.

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Of course, we should not take the foregoing calculation of the cost of sex too literally. Seed and pollen production may not be exactly proportional to the amount of resources devoted to these processes, and this can have a substantial effect on evolutionary outcomes (CHARLESWORTH and CHARLESWORTH 1981; CHARNOV 1982). Furthermore, there are various costs associated with sex that have not been incorporated, such as the danger of suffering a loss of fitness due to a sexually transmitted disease. Nevertheless, there is empirical support for the idea that pollen production produces a very substantial decrease in the potential fertility of a population. For example, in gynodioecious plant species where some individuals (females) produce seeds but no pollen, and others produce both seeds and pollen (hermaphrodites), the seed output of hermaphrodites is typically well below that of females (LLOYD 1976; ASSOUAD *et al.* 1978; VAN DAMME and VAN DELDEN 1984).

Given the foregoing considerations, it seems reasonable to expect that, in a competition between two partially asexual species, the winner will be the species that produces the smaller proportion of seeds sexually (the smaller ϕ value). Thus, we might expect obligately sexual outbreeding species to be extremely rare, or absent.

The large number of obligate (or nearly obligate) outbreeding sexual species suggests that sex confers some ecological benefits that provide a counterweight to the cost of sex, which in the foregoing example is embodied by expenditure of resources on pollen production. The possible nature of these benefits has occupied a great deal of attention among theoreticians and experimentalists (MICHOD and LEVIN 1988). One of the earliest ideas was that sex provides benefits by allowing beneficial mutations that arise in different individuals to be combined in a single genome. Although the origin of this idea dates back at least to WEISMAN (1889), it is usually attributed to FISHER (1930) and to MULLER (1932), and is sometimes called the Fisher-Muller Hypothesis. Another venerable evolution-of-sex theory has it that sex helps to slow genetic deterioration due to random increases in the frequencies of deleterious mutations. This idea was proposed by H. J. MULLER in the 1960's, and it is generally known as Muller's Ratchet (MULLER 1964; FELSENSTEIN 1974; HAIGH 1978; PAMILO *et al.* 1987; BELL 1988; LYNCH and GABRIEL 1990; CHARLESWORTH *et al.* 1993; GABRIEL *et al.* 1993; KONDRASHOV 1994). A variety of other theories have also used deleterious mutations in attempts to account for the evolution of sex (BERNSTEIN *et al.* 1988; KONDRASHOV 1988; MICHOD and GAYLEY 1992). In addition, it has been suggested that sex confers an enhanced ability to survive attacks by parasites (HAMILTON *et al.* 1990).

Theoretical studies have shown that some of the mechanisms proposed to account for the evolution and maintenance of sexual reproduction can produce benefits of sufficient magnitude to overcome the twofold cost of sex (MICHOD and LEVIN 1988). In other words, in some cases we can expect an obligately sexual species to win competitions with obligately asexual species in spite of the tendency of sexual species to divert large amounts of resources to "male effort" such as pollen production. However, this does not necessarily mean that a sexual species will really win against all comers. For example, the Fisher-Muller Hypothesis can produce large benefits for a sexual species that is in competition with an asexual species (FELSENSTEIN 1974; PAMILO *et al.* 1987). However, it appears a small amount of sexual reproduction would be required to rid a population of virtually all of the interference between beneficial mutations that is described by the Fisher-Muller Hypothesis (MAYNARD SMITH and HAIGH 1973; PAMILO *et al.* 1987). Thus, even if ϕ is small (but positive) we can expect that most beneficial mutations that arise in different individuals and that increase to a nonnegligible frequency will eventually be combined into the same genomes. Therefore, it seems likely the rate of accumulation of beneficial mutations would be very similar for a species that produces only 20% of its seeds sexually ($\phi = 0.2$) and one that is obligately sexual ($\phi = 1$).

A small difference in the rate of accumulation of beneficial mutations could eventually produce large and sustained differences in the fitness of two species. However, if there is no change in selection pressures, then this would require that there is no practical limit to the improvements that can be made to certain loci. If there were a limit, then, in a typical Fisher-Muller model, where only beneficial mutations are considered (FELSENSTEIN and YOKOYAMA 1976; PAMILO *et al.* 1987), both of the competing species would eventually reach the same asymptotic fitness. This "no-limit" requirement can be relaxed if changes in the direction of selection are allowed. However, these changes would have to be frequent enough to avoid an approach to the asymptotic fitness, and yet infrequent enough so that the small difference in the rate of accumulation of beneficial mutations can effect a large difference in fitness.

It is not just the Fisher-Muller Hypothesis that is susceptible to this sort of criticism. For example, a similar critique can be constructed for the Muller's Ratchet theory. A recent study of Muller's Ratchet by CHARLESWORTH *et al.* (1993) suggests that a species with a relatively low rate of recombination can achieve nearly as great a benefit as a species with a high rate of recombination with respect to the rate of accumulation of deleterious mutations. This suggests that species with low (but positive) values of ϕ will not suffer from a substantially greater rate of accumulation of deleterious mutations than obligately sexual species, so long as linkage is not too tight. A similar conclusion is obtained by examination of simulation results produced by PAMILO *et al.* (1987). Given the costs associated with high values of ϕ, this leads once again to the question of how obligate (or near-obligate) sexuality is maintained.

Most of the traditional evolution-of-sex theories have only been examined in the context of contests between obligately sexual and obligately asexual species. Nevertheless, it is certainly possible that one or more of them can be used to show how obligately sexual species can prevail in between-species competitions with species that produce some, but not all of their offspring asexually. However, in light of the foregoing discussion, it seems unlikely that either the Fisher-Muller Hypothesis or Muller's Ratchet will prove satisfactory in this regard. Additional research will be required to determine whether any of the traditional evolution-of-sex models can provide a mechanism whereby obligately sexual species can out-compete species with all other mating systems. For further discussion of this issue, see recent papers by GREEN and NOAKES (1995), and by HURST and PECK (1996).

In this paper we shall study a new model in an attempt to show how obligate (or nearly obligate) sexual reproduction can succeed in between-species contests. Our study focuses on a process whereby suboptimal genes can rise to a high frequency as a result of genetic drift. Although each imperfect gene may, by itself, cause only a very small decrement in fitness, a genome full of slightly imperfect genes can have an enormous effect. The decrease in fitness due to random changes in frequency of imperfect genes is known as drift load (KIMURA and OHTA 1970). Our simulation results provide evidence to support the idea that drift load can be much less debilitating in sexual, as compared to asexual species. We also show that drift load can be substantially less debilitating in obligately sexual species, as compared to species that produce only some of their offspring sexually, and the rest asexually ($0 < \phi < 1$). Thus, drift load may be a critical factor that allows for the evolution and persistence of obligate sexuality.

A MODEL OF MUTATION, REPRODUCTION AND SELECTION

The nuclear genome consists of long chains of nucleotides on chromosomes. A variety of different types of mutational events can alter the genome, including excisions, insertions and point mutations. Many of these changes will have no effect on phenotype (that is, on the nature and quantity of the various gene products) (KIMURA 1983). It is plausible that other changes will alter phenotype, but will not cause any change in fitness. Finally, there is a third set of changes that do alter fitness. We will refer to mutations of this sort as FAMs (for fitness-altering mutations).

What is the distribution of selective effects of FAMs? There is not enough data to make any precise and confident statements in answer to this question. However, we do know that, at least in Drosophila, mutations that decrease fitness by 2 or 3% are common (MUKAI *et al.* 1972). Many theoretical studies of the effects of mutation and selection have noted this fact, and then made the simplifying assumption that all mutations are deleterious (*e.g.*, KONDRASHOV 1984; CHARLESWORTH *et al.* 1993). However, this assumption is problematic, as it tends to lead to a situation where, in any finite population, there is a continual degeneration of mean fitness as deleterious mutations drift to fixation (*e.g.*, CHARLESWORTH *et al.* 1993). Admittedly, the rate of fixation of deleterious mutations can be very low if all mutations have a substantial effect on fitness. However, if deleterious mutations of small effect are allowed, then fixations can occur much more frequently, but the deterioration of mean fitness may still be slow, because each fixation will have only a small effect (CHARLESWORTH *et al.* 1993). KONDRASHOV claims to have shown that the deterioration of fitness can be slowed to a near (but not complete) stop if mutations combine synergistically, so that each additional mutation causes a larger decrease in fitness (KONDRASHOV 1994). However, it seems certain that KONDRASHOV would have come to very different conclusions if he had allowed for the existence of a class of very-small-effect mutations (BUTCHER 1995). The existence of such a class of mutations seems likely, given current data (see, for example, MACKAY 1992; OHTA 1992; KEIGHTLEY 1994). Thus, for the present, it may be reasonable to reject any model of evolution in finite populations that allows only deleterious mutations, because the resulting inexorable deterioration of mean fitness is at odds with the observation that life persists on earth after billions of years of evolution.

One might seek to correct deleterious-mutation-only models by assuming that beneficial mutations arise at some fixed rate. However, this approach would probably prove unsatisfactory, because it seems unlikely that fixation of beneficial mutations would precisely counterbalance the deterioration of mean fitness caused by deleterious mutations, and so no stationary distribution would be reached. Rather, we would be likely to arrive at a situation where mean fitness deteriorates despite the beneficial mutations, or where fitness increases steadily to unrealistic levels. Thus, it is necessary to find a model in which the rates and magnitudes of deleterious mutations and beneficial mutations are coupled.

There are a variety of ways to achieve the required coupling of rates and/or magnitudes for deleterious and beneficial mutations. For example, one can assume a house-of-cards model, in which the selection coefficient associated with a new mutation is drawn from a distribution that is unrelated to the selection coefficient of the allele as it was before the mutation (KINGMAN 1978). This leads to a situation where genes that confer a high level of fitness tend to sustain deleterious mutations, whereas highly deleterious genes have a relatively large probability of sustaining beneficial mutations. Approaches of this sort have recently been explored by a number of researchers (BARTON 1986; OHTA and TA-

CHIDA 1990; TACHIDA 1991; ZENG and COCKERHAM 1993). The house-of-cards model is analytically convenient. However, it is also biologically unrealistic because, when a gene mutates, it is unreasonable to expect that the premutation state of the gene will bear no relation to the postmutation state. Furthermore, house-of-cards models can be problematic in simulation studies because, when they are used, it can take a very long time to approach a stationary distribution. This was observed by TACHIDA (1991), who used a normal distribution of mutant effects. We have observed the same phenomenon both with normal distributions, and with uniform distributions of mutant effects.

Instead of the house-of-cards model, we constructed a model of mutation that is based on the ideas of R. A. FISHER (1930). This model allows for both beneficial and deleterious mutations, and mutant effects are biased so that there is a correlation between the state of an allele before mutation, and its postmutation state. Furthermore, in our particular version of the Fisherian mutation model, a substantial fraction of mutations produce a very small change in fitness. This property of the model is in accord with what limited data there is (see, for example, MACKAY 1992; OHTA 1992; KEIGHTLEY 1994). The tendency of our mutation model to produce very small changes in fitness tends to speed the approach to stationary distributions, and these small-effect mutations are one factor that distinguishes our model from a one-locus model of mutation that was produced by ZENG and COCKERHAM (1993). However, ZENG and COCKERHAM's model, like our own, allows for correlations between premutation and postmutation allelic effects. Both ZENG and COCKERHAM's model and our own are related to a model presented in a mathematical appendix of a paper by LYNCH and GABRIEL (1990).

The mutation and selection scheme used here is similar, in many ways, to models that have traditionally been used in quantitative genetics (see BULMER 1989 and references therein). In general, these models employ mutation schemes that make beneficial mutations increasingly more likely as individuals become less fit. However, these models generally assume a Gaussian selection scheme, while we make a much simpler assumption, which is that allelic affects combine multiplicatively to determine fitness.

To describe the Fisherian mutation scheme in detail, we must first make some assumptions about the nature of reproduction and selection. There are a wide variety of models to choose from, but for the sake of simplicity and concreteness, let us concentrate on the case of fertility selection in a diploid population of annual seed-bearing plants. Assume that all reproductively mature population members (*i.e.*, adults) are capable of producing seeds. Seed production can be accomplished either sexually or asexually. Each adult is assumed to produce a very large (effectively infinite) number of seeds, and a proportion ϕ of these seeds is produced by sexual means, while the rest are produced asexually (where $0 \leq \phi \leq 1$). If $\phi > 0$ (so that some seeds are produced sexually), then each adult individual is assumed to produce pollen, in addition to seeds. The number of pollen grains that an individual produces is assumed to be proportional to the number of seeds produced by that individual. Furthermore, the coefficient of proportionality is assumed to be sufficiently large so that there are always enough pollen grains available for all fertilizations.

When adults generate seeds sexually, they produce an ovule, and in general, this is fertilized by a pollen grain that is randomly selected from the total collection of pollen grains produced in the population during that generation. However, if the pollen grain selected is from the same individual that produced the ovule, then the pollen grain is rejected and another is selected at random (thus, selfing is not allowed). Standard Mendelian segregation and recombination without interference is involved in the production of both ovules and pollen. When an adult produces a seed asexually, it simply copies its genetic material into the seed, so that the seed and its parent are genetically identical, except for new mutations.

After seed production, N seeds are selected at random, and these germinate and grow to reproductive maturity. Thus, N is the size of the adult population.

In light of the foregoing assumptions, it should be clear that an adult's fitness is proportional to the number of seeds that the adult produces. That is to say, the number of seeds that an individual produces is proportional to the expected number of seeds that will grow to maturity to which the individual contributes genetic material.

Assume that the number of seeds produced by an individual depends only on the individual's genotype. Let L represent the number of sites within the genome that are subject to FAMs. That is, L is the number of sites within a haplotype that are subject to selection. Some of these sites may lie within noncoding regions of the DNA, since it is known that mutations in these regions sometimes have substantial phenotypic effects (TURELLI 1984; KONDRASHOV 1988; KONDRASHOV and TURELLI 1992; NOWAK 1994). In addition, there are likely to be multiple sites within many genes that are subject to FAMs. Thus, the number of sites within the genome that are susceptible to FAMs may be much larger than the number of genes. Nevertheless, for convenience, we will use the word "allele" to refer to one of the alternative sequences at a given site.

Let r represent the rate of recombination between adjacent sites on a chromosome. Assume that there are H independently segregating chromosomes within the genome, and that an equal number of sites lie on each chromosome (thus, L must be a multiple of H).

Let us assume a multiplicative model of fitness determination. This model is, conceptually, the simplest one

possible, as it allows us to assign a selection coefficient to each allele that can occur at a site. There is also some support for a multiplicative model from MUKAI's classic set of experiments (MUKAI *et al.* 1972). However, MUKAI's results might also be said to support an additive model, since the multiplicative and the additive models are very similar if the selection coefficients involved are sufficiently small. Nevertheless, the additive model can give negative fitness values, which are impossible in discrete-time models like ours. Thus, we prefer a multiplicative model.

Because the population is diploid, each site under selection occurs twice within the genome. Number the occurrences of each site as 1 and 2, in arbitrary order. Assume that the state of each of an individual's $2L$ sites can be represented by a real number x, where $-\infty < x < \infty$. Assume further that the optimum state for each allele is achieved when $x = 0$. Let $d_{i,j,k}$ represent the absolute value of the deviation from the optimum state of the allele at the jth occurrence of the ith site in the kth adult for a particular generation (*i.e.*, $d_{i,j,k} = |x|$). Let D_k represent the sum of these deviations for the kth adult. That is,

$$D_k = \sum_{i=1}^{L} [d_{i,1,k} + d_{i,2,k}]. \tag{1}$$

Let w_k represent the fertility (and thus the fitness) of the kth adult during a particular generation, relative to an adult with the optimal genotype (where $1 \leq k \leq N$). (The optimal genotype is one for which $x = 0$ for all $2L$ alleles that are under selection). This is to say, w_k is proportional both to the number of seeds that an individual produces, and proportional to the number of pollen grains that an individual produces. The value of w_k is assumed to depend on D_k as follows:

$$w_k = \exp(-D_k). \tag{2}$$

To make the multiplicative nature of the model more apparent, this can be rewritten as

$$w_k = \prod_{i=1}^{L} [\exp(-d_{i,1,k}) \exp(-d_{i,2,k})]. \tag{3}$$

This can be rewritten yet again in terms of traditional selection coefficients. If we define $s_{i,j,k}$ to be the selection coefficient associated with the jth occurrence of the ith site in the kth adult in a particular generation, then we have

$$s_{i,j,k} = 1 - \exp(-d_{i,j,k}). \tag{4}$$

Thus we have $0 \leq s_{i,j,k} < 1$, and the selection coefficient associated with a particular allele is equal to zero when $d_{i,j,k}$ equals zero, and it tends toward 1.0 as $d_{i,j,k}$ tends toward infinity. Note that Equation 3 can be rewritten in terms of selection coefficients as follows:

$$w_k = \prod_{i=1}^{L} (1 - s_{i,1,k})(1 - s_{i,2,k})]. \tag{5}$$

It is worth noting that the scheme for determining fitness that is specified by Equation 5 involves some degree of dominance. Thus, if we consider two alleles (A_1 and A_2) with selection coefficients s_1 and s_2, then we will find that the fitness of an A_1A_2 heterozygote is not the arithmetic average of the fitness of the A_1A_1 homozygote and the fitness of the A_2A_2 homozygote (assuming that the rest of the genotype is the same at all other loci for both homozygotes, and for the heterozygote). Dominance disappears, however, if we measure the logarithm of fitness, rather than fitness itself.

We can now turn to a detailed description of the Fisherian mutation process. For sexually produced seeds, mutations occur during gamete formation. For asexually produced seeds, mutation occurs during seed production. The probability that any given allele that is incorporated into a seed will have just undergone a mutation is assumed to be independent of the mode of seed production, and it is represented by μ (*i.e.*, μ is the allelic mutation rate). A mutation is assumed to change the value associated with an allele by an amount m, such that the mutated value of the allele is given by $x = m + x^*$, where x^* is the value of x that would have been associated with the allele if no mutation had occurred (*i.e.*, x^* is the parental value of x for the allele in question).

The distribution of m used in the simulation studies is a "reflected gamma" distribution. This distribution has been used to model mutations of genes that control quantitative characters (KEIGHTLEY and HILL 1987; KEIGHTLEY and HILL 1988; see also KIMURA 1983, p. 241; HILL and RASBASH 1986). In generating the reflected gamma distribution, we follow KEIGHTLEY and HILL's example, and use a gamma distribution with shape parameter $^1/_2$ (KEIGHTLEY and HILL 1987). This ensures that a considerable proportion of mutations will have a very small effect, while others will have a substantial effect. That is to say, the distribution is leptokurtic. This sort of distribution is in line with current data on the effects of mutations (MUKAI *et al.* 1972; MACKAY *et al.* 1992; OHTA 1992; KEIGHTLEY 1994).

In the reflected gamma distribution used in this paper, the density function for positive values of m is given by

$$f(m) = \frac{\alpha^{1/2} e^{-\alpha m} m^{-1/2}}{2\Gamma(1/2)}. \tag{6}$$

where $\Gamma(^1/_2)$ is a gamma function with parameter $^1/_2$. For all $m > 0$, this distribution has half the height of a gamma distribution with shape parameter equal to $^1/_2$. Similarly, the density function for negative values of m is as follows:

$$f(m) = \frac{\alpha^{1/2} e^{\alpha m} |m|^{-1/2}}{2\Gamma(1/2)}. \tag{7}$$

Thus, the entire distribution is symmetric about zero,

and so the expected value of m is zero. The expected value of m given that m is positive is $1/(2\alpha)$. Thus, α sets the scale of the distribution. It should be clear that the expected absolute value of m is also given by $1/(2\alpha)$. For this reason, we will use $|m|$ to represent the value of $1/(2\alpha)$. In words, $|m|$ represents the average effect of mutations.

Under the above-specified set of assumptions governing mutation, reproduction and selection, only deleterious mutations are possible when an allele is in its optimal state. On the other hand, beneficial mutations (*i.e.*, mutations that reduce the selection coefficient against an allele) become more likely as an allele becomes less perfect (*i.e.*, as $|x|$ becomes large). Indeed, as $|x|$ tends toward infinity, the probability that any new mutation will be beneficial tends toward $^1/_2$. These characteristics are in line with Fisher's ideas about the nature of FAMs (FISHER 1930; KIMURA 1983).

PROCEDURES FOR THE SIMULATIONS STUDIES

Let us now move on to consideration of the simulation studies. Before presenting the results of the simulations, we will explain the methods used and the reasoning that led to the selection of the particular parameter values that were employed.

Choice of parameter values: As we have seen, data on Drosophila suggest that mutations that decrease fitness by ~2% are common. Therefore, for most of the simulation studies presented in this paper, we set α so that the average effect of a mutation to a perfect allele ($x = 0$) is to decrease fitness by 2%. Using Equation 4, it is straightforward to show that this is achieved when $|m| = 0.0206$, and this means $\alpha = 24.253$. A reflected gamma distribution with this value of α is shown in Figure 1.

What value of L (the number of sites) should be used in the simulation studies? It is clear that a very large number of different sites in the genome are capable of sustaining FAMs. For example, in Drosophila, it appears that there are ~10,000 genes (KONDRASHOV 1988). In mice and humans it appears that there are ~80,000 genes (ANTEQUERA and BIRD 1993). In addition, it is likely that nearly all intact genes are susceptible to FAMs. This assertion is based on the idea that, if an intact gene was not susceptible to FAMs, then it would probably accumulate frame-shift mutations or other mutations that prevent expression, and so become a pseudogene. Furthermore, as mentioned earlier, the number of sections of DNA that are capable of sustaining FAMs is probably far in excess of the number of genes capable of sustaining FAMs. This is because there are sites in noncoding regions of the genome that can sustain FAMs (TURELLI 1984; KONDRASHOV 1988; KONDRASHOV and TURELLI 1992; NOWAK 1994) and there are probably multiple fitness-affecting sites within many genes, each of which is capable of sustaining FAMs.

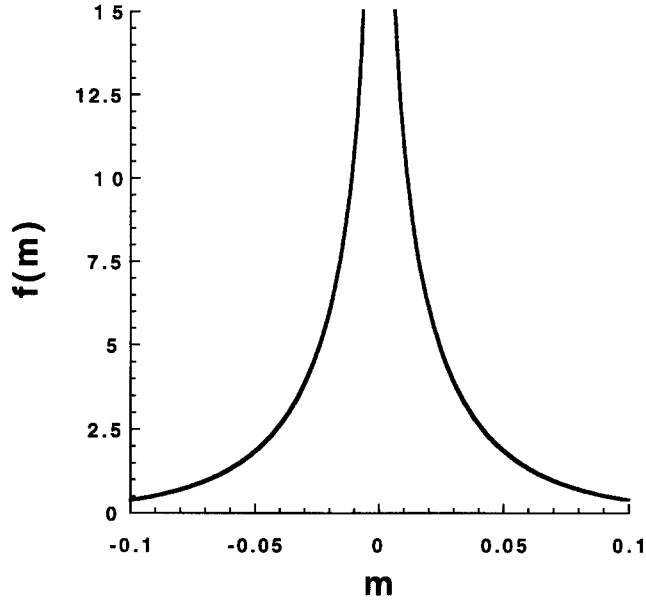

FIGURE 1.—The distribution of m used in the simulation studies. This is a reflected gamma distribution (see Equations 6 and 7). The value of α is set to 24.253. This ensures that the average selection coefficient associated with a perfect allele ($x = 0$) that has undergone a single mutation is $s = 0.02$.

Despite the large number of fitness-controlling mutable sites that are present in most organisms, there are severe limits on the number of mutable sites that can be accommodated in a usable computer simulation program. For most of the simulations, we compromised by using 1000 sites ($L = 1000$).

Next, let us consider what value of μ (the allelic mutation rate) is reasonable for use in the simulations. Unfortunately, there is no hope of using a biologically realistic value for this parameter (say between 10^{-9} and 10^{-5}), because the simulations would take much too long to run. Even if such a low value could be used, the genomic rate of mutation (*i.e.*, the rate per diploid genome) would be too low because we are unable to run the simulations with more than a few thousand sites. The genomic rate of mutation may be more important than the allelic rate, as it can have a strong effect on genetic load (KIMURA and MARUYAMA 1966). Therefore, we will seek to employ a value of μ that gives a reasonable value for the genomic rate of mutation.

Let U represent the genomic rate of fitness-altering mutations (thus, $U = 2L\mu$). There has been a substantial amount of work carried out to establish the value of U in Drosophila, and there has also been some work on plants (MUKAI 1964; MUKAI *et al.* 1972; CROW 1979; KONDRASHOV 1988; CHARLESWORTH *et al.* 1990; KONDRASHOV and TURELLI 1992). According to KONDRASHOV and TURELLI (1992) the data on multicellular eukaryotes are consistent with any value of U between 0.1 and 100. However, we think that the lower end of this range ($U \approx 0.1$) is extremely implausible in light of the experimental data (for example, see MUKAI *et al.* 1972;

CHARLESWORTH *et al.* 1990; 1992). Furthermore, it is important to recognize that laboratory experiments typically focus on only one or two components of fitness, and that many deleterious mutations may not be apparent under laboratory conditions (SIMMONS and CROW 1977; CROW and SIMMONS 1983; KONDRASHOV and TURELLI 1992).

In light of the data just cited, it seems likely that $U > 1$ applies in natural populations of Drosophila, and probably in a wide variety of other higher organisms as well. This impression is strengthened if we accept the idea that a substantial fraction of FAMs will have a very small effect on fitness, while others will alter fitness by 2% or more. The presence of this sort of variation should increase our estimate of U because variance in selection coefficients tends to cause underestimates of the value of U for purely mathematical reasons (MUKAI *et al.* 1972; HOULE *et al.* 1992), and because small-effect mutations may go unnoticed in laboratory experiments. As pointed out previously, the idea that many FAMs have a very small effect on fitness is consistent with existing data. Such an assumption is also consistent with the distribution of mutant effects used in our model. For example, with the distribution of m values shown in Figure 1, the average mutation to a perfect allele will decrease fitness by 2%. However, 24% of the time a mutation will decrease fitness by less than 0.2% ($s < 0.002$). Furthermore, 8% of the time, a mutation will decrease fitness by less than 0.02% ($s < 0.0002$).

With these considerations in mind, we decided to run most of our simulations with $U = 2.0$. If $L = 1000$, this means $\mu = 0.001$. Given the data cited above and our leptokurtic mutation function, a higher value of U might be justified. However, our preliminary studies suggested that high values of U tend to produce an advantage for obligate (or near obligate) sexuality, and so a relatively low value of U is conservative in the context of a theory of the evolution of sex.

Before we could proceed with the multi-locus simulations, we had to make some choices with regard to the number of chromosomes (H) and the rate of recombination between adjacent sites under selection (r). In doing this, we used the mouse genome as a guide, since it is relatively well studied and seems fairly typical for an animal or higher plant with regard to the total map distance in the genome (1600 cM) and the number of chromosomes ($H = 20$) (DAVISSON and RODERICK 1990; SHIELDS 1993). With this in mind, we used $H = 20$ independently segregating chromosomes in all of the simulations. For simplicity, we assumed that the rate of recombination (r) was the same between all adjacent sites.

What value of r is most realistic for use in the simulations? Unfortunately, existing data is much too poor to provide a reliable answer to this question. However, in higher plants the rate of recombination between adjacent nucleotides is typically in the range 10^{-9}–10^{-7} (SHIELDS 1993). Similar values probably hold in many animals. Thus, values in this range provide a lower bound for the average rate of recombination between adjacent sites. The rate of recombination between sites that are at opposite ends of a typical gene that is a few kb in length would be on the order of 10^{-5}. Furthermore, we can estimate the average rate of recombination between adjacent genes in the mouse by dividing the total map length of the mouse genome (1600 cM) by the estimated number of genes [80,000 (ANTEQUERA and BIRD 1993)] to produce an estimated average rate of recombination between adjacent genes of 0.0002.

As mentioned above, it seems likely that nearly all genes are under some sort of selection, so 0.0002 is a reasonable upper bound for the average distance between sites. Nevertheless, with only 1000 sites in the genome, using $r = 0.0002$ as the rate of recombination between adjacent sites may be problematic, as it implies an unrealistically low rate of recombination between sites at opposite ends of the chromosome. We can correct for this by distributing the sites evenly across chromosomes (with 50 per chromosome) and assuming a total map distance of 80 cM per chromosome (the average for mice). This results in a rate of recombination between adjacent sites of ~0.016. Of course, this "correction" is itself problematic, as the average rate of recombination between adjacent selected sites in most real organisms must be much lower than 0.016. With these considerations in mind, we used $r = 0.016$ in most of the simulations, but we also tested the effects of lower and higher values of r.

Standard parameter values: As explained above, most of our simulations used $|m| = 0.0206$. This should be considered to be the standard value of $|m|$, and this standard value was used in every simulation reported in this paper, unless a different value is given explicitly. Similarly, the standard value for the number of sites is $L = 1000$ and the standard value for the rate of recombination between adjacent sites is $r = 0.016$. The standard value for the allelic rate of mutation is $\mu = 0.001$, and this means that the standard genomic rate of mutation is $U = 2.0$. The standard value for the number of generations run in a simulation trial is 100,000, and the standard number of generations over which the output statistics are calculated is 50,000 (*i.e.*, data was collected during the last 50,000 generations of the trial). The standard value for the size of the population is $N = 100$. In all cases, the standard values were used unless different values are explicitly given.

Initialization, data collection and descriptive statistics: Simulation trials were initialized by generating a population of N individuals, each of which had a perfect genotype (*i.e.*, $x = 0$ for all alleles, and thus $D_k = 0$ for $i = 1, 2, \ldots, N$).

As mentioned above, most of the simulation trials were run for 100,000 generations, and data for calculation of the output statistics was generally collected for

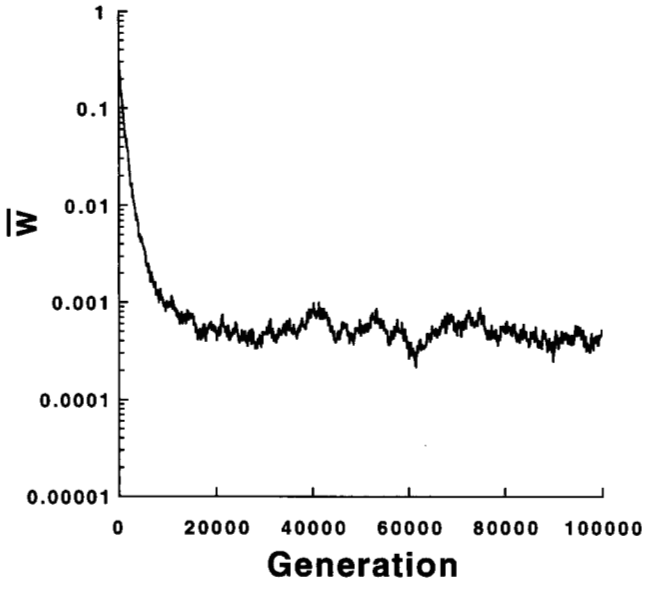

FIGURE 2.—The change in $\bar{w}$ over the course of a single trial. For this trial, the parameters were set to their standard values. Thus, $|\bar{m}| = 0.0206$, $L = 1000$, $r = 0.016$, $U = 2.0$ and $N = 100$. We also set $\phi = 1.0$, so the population was obligately sexual. The data are presented on a log scale.

the last 50,000 of these generations. From an evolutionary perspective, we should be most interested in the behavior of a population once it has achieved a stationary distribution and is no longer under the influence of the initialization conditions. We found that the slowest approach to a stationary distribution seemed to occur for the largest values of ϕ. Therefore, to demonstrate that 50,000 generations is sufficient to produce what appears to be a stationary distribution, we ran a trial using the standard values, and setting $\phi = 1$. We plotted the resulting mean finesses over the course of the generations. The data are presented in Figure 2. Mean fitness is represented by $\bar{w}$, and the value of $\bar{w}$ for a particular generation was calculated by averaging the w_k values over all of the adults present during that generation. Thus, we have $0 < \bar{w} \leq 1$. As can be seen from the graph, the $\bar{w}$ values do not seem to be undergoing any directional change after the first 20,000 generations. We took various other measures of the population, and these produced similar results. We also kept track of the number of $x = 0$ alleles present in the population. All of these were gone from the population and had been replaced by alleles for which $|x| \neq 0$ by generation 21,900. Taken together, these observations suggest that, for the standard parameter values, 50,000 generations is more than enough to establish a stationary distribution, and thus it appears that we were justified in our decision to begin calculating the output statistics after 50,000 generations had elapsed.

Despite this apparent lack of directional change after 50,000 generations, there is considerable variation between generations in $\bar{w}$. Therefore, we calculated additional statistics. The first of these is called $\bar{\bar{w}}$, and it is the arithmetic mean of the $\bar{w}$ values over the last 50,000 generations of a trial. Thus, to calculate $\bar{\bar{w}}$ under the standard value of 100,000 generations per trial, we summed up the $\bar{w}$ values from generations 50,001 until generation 100,000, and divided the result by 50,000.

While $\bar{\bar{w}}$ is a convenient descriptive statistic, the geometric mean of the $\bar{w}$ values over time should be a better indicator of the ability of a species to compete against other species than is the arithmetic mean. Therefore, we calculated $\bar{\bar{w}}_g$, which is the geometric mean of the $\bar{w}$ values during the last 50,000 generations of a trial. Experience with the model revealed that, in general, the $\bar{\bar{w}}$ values obtained from running the program were within a few percent of the corresponding $\bar{\bar{w}}_g$ values obtained (although the $\bar{\bar{w}}$ values were always higher than the corresponding $\bar{\bar{w}}_g$ values, and this must be so whenever there is variation over time in the $\bar{w}$ values). With these observations in mind, we decided to concentrate on the $\bar{\bar{w}}_g$ values in this paper, and we largely ignore the $\bar{\bar{w}}$ values.

Between-population differences in fitness are caused by differences in the distributions of selection coefficients. To characterize these values, during each generation we calculated the mean selection coefficient, averaging over all of the alleles present in the population (selection coefficients were calculated using Equation 4). The mean selection coefficient is called $\bar{s}$.

Naturally, $\bar{s}$ varies from one generation to the next, just like $\bar{w}$. Therefore, for each trial, we calculated an additional statistic, called $\bar{\bar{s}}$, which is the arithmetic mean of $\bar{s}$, calculated over the last 50,000 generations of the trial.

Another statistic calculated during the simulation trials was the coefficient of variation of the w_k values. This quantity may be represented as V_w. It is calculated by dividing the standard deviation of the w_k values for a given generation by the value of $\bar{w}$ for that generation, and then multiplying the result by 100. Thus, $V_w/100$ is simply the standard deviation of relative fitness, where relative fitness is measured as relative to $\bar{w}$.

The arithmetic average of V_w was calculated over the same generations for which the $\bar{\bar{w}}_g$ and $\bar{\bar{s}}$ values were calculated (*i.e.*, the last 50,000 generations of a trial). This average is denoted by $\bar{V}_w$.

As we noted in the Introduction, the more sexual a species is, the more it is likely to suffer a fertility loss because of the expenditure of resources on pollen. For the purposes of some comparisons, it is useful to take this source of fertility differences into account. The $\bar{w}$ values are not corrected for this source of differential fertility.

As we have seen, a rough-and-ready guess as to the magnitude of the decrease in seed output as a result of pollen production is given by $[1 - (\phi/2)]$. With this in mind, we calculated a corrected measure of fitness, to be called $\bar{w}_c$. The value of $\bar{w}_c$ is given by

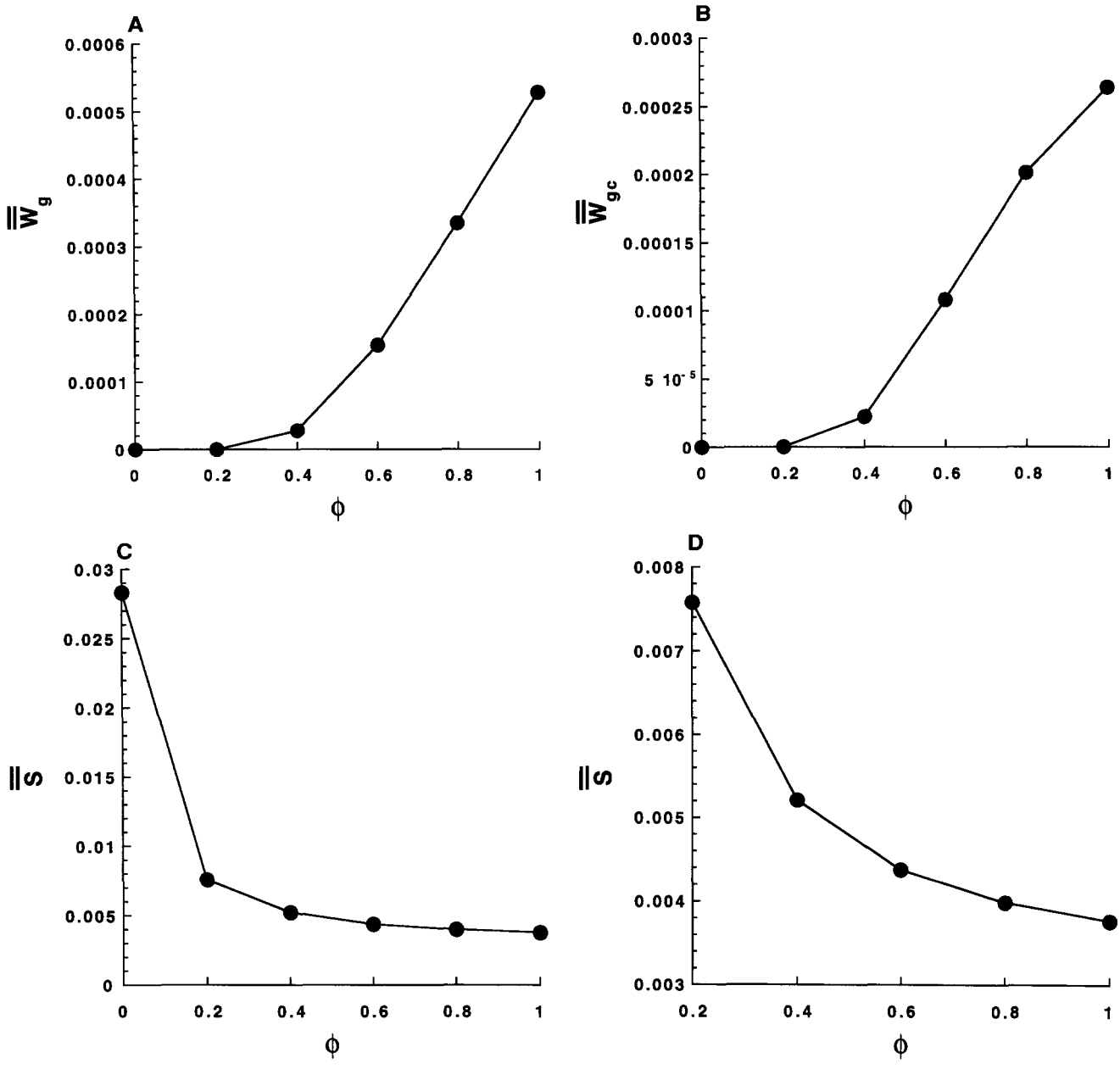

FIGURE 3.—Results from the simulations when the standard parameter values were in force. A shows the change in $\bar{w}_g$ as ϕ (the proportion of offspring produced sexually) goes from 0 to 1. B shows the effect of ϕ on $\bar{w}_{gc}$. C shows the effect of ϕ on $\bar{s}$, while D shows the same data, except that the scale on the ordinate is expanded, and the data point for $\phi = 0$ has been left off. In all four panels, the data points represent the mean values for the two replications run (the corresponding standard errors are given in Table 1).

$$\bar{w}_c = \left[1 - \frac{\phi}{2}\right]\bar{w}. \tag{8}$$

Similarly, we can modify the value of $\bar{w}_g$ to account for the cost of sex. The modified value is called $\bar{w}_{gc}$, and it is given by

$$\bar{w}_{gc} = \left[1 - \frac{\phi}{2}\right]\bar{w}_g. \tag{9}$$

Comparison of $\bar{w}_{gc}$ values is particularly revealing. This measure is not very susceptible to random fluctuations, and if two similar species that are competing for some resource have different $\bar{w}_{gc}$ values, then, all else being equal, we can expect the one with the higher value to win the between-species competition. This is so even if the two species have different values of ϕ, and thus different allocations of resources to pollen and seed production. Furthermore, the ratio of the $\bar{w}_{gc}$ values for two different species provides an estimate of the ratio of the per-capita rates of seed production for those two species. This said, it is important to recognize that "all else" will not necessarily be equal, and this is considered further in the discussion section.

TABLE 1

Computer simulation results

ϕ values and changes from standard parameter values	$\bar{w}_g$	$\bar{w}_{gc}$	$\bar{V}_w$	Mean no. of segregating alleles	$\bar{s}$
$\phi = 1$	0.000527	0.000263	18.9	2.63	0.00376
	(3.49×10^{-6})	(1.75×10^{-6})	(0.0100)	(0.00100)	(3.39×10^{-6})
$\phi = 0.8$	0.000335	0.000201	18.8	2.59	0.00399
	(4.55×10^{-7})	(2.74×10^{-7})	(0.0300)	(0.00100)	(7.50×10^{-7})
$\phi = 0.6$	0.000154	0.000108	18.6	2.53	0.00437
	(2.47×10^{-6})	(1.73×10^{-6})	(0.0150)	(0.000501)	(7.95×10^{-6})
$\phi = 0.4$	2.82×10^{-5}	2.25×10^{-5}	18.3	2.43	0.00521
	(4.84×10^{-7})	(3.87×10^{-7})	(0.0100)	(0.000501)	(8.56×10^{-6})
$\phi = 0.2$	2.33×10^{-7}	2.10×10^{-7}	17.6	2.28	0.00758
	(8.84×10^{-9})	(7.96×10^{-9})	(0.00501)	(0.00100)	(1.90×10^{-5})
$\phi = 0$	5.02×10^{-26}	5.02×10^{-26}	13.9	3.09	0.0283
	(8.98×10^{-27})	(8.98×10^{-27})	(0.00501)	(0.00100)	(8.30×10^{-5})
$\phi = 1$, $N = 50$	1.63×10^{-6}	8.13×10^{-7}	18.0	1.80	0.00662
	(1.99×10^{-8})	(9.96×10^{-9})	(0.0199)	(0.00100)	(6.10×10^{-6})
$\phi = 1$, $N = 200$	0.00797	0.00398	19.3	4.28	0.00241
	(2.28×10^{-5})	(1.14×10^{-5})	(0.0150)	(0.00100)	(1.46×10^{-6})
$\phi = 1$, $N = 400$	0.0337	0.0169	19.6	7.57	0.00169
	(0.000709)	(0.000355)	(0.0100)	(0.00199)	(1.05×10^{-5})
$\phi = 1$, $L = 240$	0.0488	0.0244	18.2	7.23	0.00626
	(0.000267)	(1.34×10^{-4})	(0.00501)	(0.00601)	(1.14×10^{-5})
$\phi = 1$, $L = 500$	0.00965	0.00483	18.7	4.16	0.00462
	(5.28×10^{-6})	(2.64×10^{-6})	(0.0100)	(0.00351)	(4.99×10^{-7})
$\phi = 1$, $L = 2000$	1.75×10^{-6}	8.73×10^{-7}	19.0	1.83	0.00330
	(2.38×10^{-8})	(1.19×10^{-8})	(0.0150)	(0.00100)	(3.45×10^{-6})
$\phi = 1$, $U = 1$	0.00156	0.000781	13.4	1.86	0.00322
	(1.56×10^{-5})	(7.76×10^{-6})	(0.0100)	(0.00150)	(4.89×10^{-6})
$\phi = 1$, $U = 4$	4.45×10^{-5}	2.23×10^{-5}	26.4	3.97	0.00499
	(6.84×10^{-7})	(3.42×10^{-7})	(0.0250)	(0.00199)	(7.59×10^{-6})
$\phi = 1$, $U = 8$	5.55×10^{-7}	2.78×10^{-7}	36.7	6.13	0.00716
	(8.40×10^{-9})	(4.20×10^{-9})	(0.0150)	(0.00150)	(7.45×10^{-6})
$\phi = 1$, $\overline{\lvert m \rvert} = 0.00201$	0.00381	0.00190	4.45	3.13	0.00278
	(0.000146)	(7.30×10^{-5})	(0.00400)	(0.00150)	(1.90×10^{-5})
$\phi = 1$, $\overline{\lvert m \rvert} = 0.0102$	0.00101	0.000503	12.6	2.86	0.00344
	(2.50×10^{-5})	(1.25×10^{-5})	(0.0199)	(0.00150)	(1.23×10^{-5})
$\phi = 1$, $\overline{\lvert m \rvert} = 0.0425$	0.000199	9.94×10^{-5}	27.1	2.37	0.00425
	(1.75×10^{-6})	(8.77×10^{-7})	(0.0250)	(0.00100)	(4.40×10^{-6})
$\phi = 1$, $\overline{\lvert m \rvert} = 0.281$	1.91×10^{-6}	9.55×10^{-7}	62.5	1.76	0.00655
	(1.47×10^{-7})	(7.35×10^{-8})	(0.0100)	(0.00100)	(3.82×10^{-5})
$\phi = 1$, $r = 0$	2.72×10^{-6}	1.36×10^{-6}	18.1	2.52	0.00637
	(1.28×10^{-7})	(6.42×10^{-8})	(0.0100)	(0.00100)	(2.33×10^{-5})
$\phi = 1$, $r = 0.0002$	1.03×10^{-5}	5.17×10^{-6}	18.2	2.53	0.00571
	(2.40×10^{-7})	(1.20×10^{-7})	(0.0250)	(0.000501)	(1.15×10^{-5})
$\phi = 1$, $r = 0.5$	0.000556	0.000278	18.8	2.64	0.00374
	(1.30×10^{-5})	(6.49×10^{-6})	(0.0150)	(0.00100)	(1.16×10^{-5})
$\phi = 1$, $E = 8$	0.139	0.0693	68.2	1.72	N/A
	(0.000316)	(0.000158)	(0.0550)	(0.00100)	
$\phi = 0.4$, $E = 8$	0.00715	0.00572	96.0	1.46	N/A
	(0.000225)	(0.000180)	(0.220)	(0.00100)	
$\phi = 0.0$, $E = 8$	1.18×10^{-10}	1.18×10^{-10}	145.0	2.30	N/A
	(9.70×10^{-12})	(9.70×10^{-12})	(0.0500)	(0.00100)	
$\phi = 1$, $E = 4$	0.0369	0.0185	58.5	1.81	N/A
	(4.00×10^{-6})	(2.00×10^{-6})	(0.0500)	(0.00100)	
$\phi = 1$, $E = 2$	0.00558	0.00279	41.0	2.06	N/A
	(4.28×10^{-5})	(2.14×10^{-6})	(0.401)	(0.000500)	
$\phi = 1$, $E = 8$, $\overline{\lvert m \rvert} = 0.005$	0.318	0.159	28.2	2.36	N/A
	(0.00148)	(0.000740)	(0.0450)	(0.000500)	
$\phi = 1$, $E = 4$, $\overline{\lvert m \rvert} = 0.005$	0.125	0.0626	24.7	2.45	N/A
	(0.00118)	(0.000591)	(0.0300)	(0.000500)	

TABLE 1

Continued

ϕ values and changes from standard parameter values	$\bar{w}_g$	$\bar{w}_{gc}$	$\bar{V}_w$	Mean no. of segregating alleles	$\bar{s}$
$\phi = 1$, $E = 2$, $\overline{\lvert m \rvert} = 0.005$	0.0224	0.0112	18.2	2.65	N/A
	(5.80×10^{-5})	(2.90×10^{-5})	(0.0100)	(0.00100)	
$\phi = 1$, $E = 1$, $\overline{\lvert m \rvert} = 0.005$	0.00185	0.000927	8.19	3.01	0.00314
	(1.90×10^{-6})	(9.50×10^{-7})	(0.00300)	(0.00100)	(5.00×10^{-7})

Each entry in the left-hand column gives the value of ϕ and any changes in the standard parameter values for the associated rows. The data shown without parentheses represent the means for two trials, while the data in parentheses gives the standard errors for the data in the preceeding row. The column entitled "mean number of segregating alleles" gives the average number of segregating alleles per selected site, averaging across all selected sites, and over the last 50,000 generation of the trials. In all cases where no value of E is given (or where $E = 1$), the data are for the multiplicative model described in the text. Where $E > 1$, the data are for the model incorporating synergistic epistasis. In the collection of data for $\bar{V}_w$ and the mean number of segregating alleles, only four significant digits were collected. Therefore, we have inflated the standard error estimates in these columns so that the figures given are equal to or greater than the standard error estimates that would have been recorded had a larger number of significant digits been collected.

All combinations of parameter values studied were used for two trials. It would have been preferable to run a large number of trials for each choice of parameter values, but this was precluded by constraints on computer time. Our decision to run two trials for each parameter set was justified by the fact that we generally found relatively small differences in the two values of $\bar{s}$ and $\bar{w}_g$ obtained. This is reflected by the size of the standard errors reported in Table 1.

RESULTS

The effects of altering the mode of reproduction (ϕ): Let us now turn to a consideration of how the mode of reproduction affects fitness. In Figure 3A the values of $\bar{w}_g$ obtained for six different values of ϕ are presented. As can be seen from the figure, the $\bar{w}_g$ values rose monotonically as ϕ increased. Although it is not apparent from Figure 3A, the increase is most dramatic between the lowest two values of ϕ used ($\phi = 0$ and $\phi = 0.2$). When $\phi = 0$, $\bar{w}_g \approx 5.02 \times 10^{-26}$, and when $\phi = 0.2$, $\bar{w}_g \approx 2.33 \times 10^{-7}$. This is an increase of more than 18 orders of magnitude. From $\phi = 0.2$ to $\phi = 1$, $\bar{w}_g$ increases further, but the increase is only ~2000-fold over this entire range (see Table 1).

Note that, in every case shown in Figure 3A, the value of $\bar{w}_g$ is far below its maximum-possible value of 1.0. This means that the results are characterized by high levels of genetic load. We shall show, in a subsequent section, that this is a consequence of the multiplicative nature of the model, and that the high levels of load can be eliminated by use of a nonmultiplicative model. Unfortunately, a nonmultiplicative model introduces a number of difficult complications, and so, in the majority of this paper, we will use a multiplicative model.

Figure 3B shows the $\bar{w}_{gc}$ values that were calculated from the $\bar{w}_g$ values shown in Figure 3A. The $\bar{w}_{gc}$ values also increase monotonically with ϕ, though the increase is less dramatic than in the case of the $\bar{w}_g$ values. This is a result of the increased cost of sex that is associated with higher values of ϕ. The monotonic increase in the $\bar{w}_{gc}$ values suggests that, under the conditions of the set of simulations from which the data were derived, obligate (or near-obligate) sex will be favored in between-species competitions.

The effect of the mode of reproduction upon $\bar{w}$ is reflected in the way that $\bar{s}$ changed with ϕ (although $\bar{w}$ also depends on linkage disequilibrium). A plot of $\bar{s}$ as a function of ϕ is shown in Figure 3C. As would be expected in light of Figure 3A, $\bar{s}$ declined monotonically with ϕ. Figure 3D shows the same data as Figure 3C, except that the range of values on the ordinate is smaller. This means that the value for $\phi = 0$ cannot be shown, but the monotonic decline in $\bar{s}$ with ϕ is much more clear.

It is worth noticing that the $\bar{s}$ values are good predictors of the $\bar{w}_g$ values. For example, if we calculate $\bar{w}$ for the case of $\phi = 1$ on the assumption that the selection coefficients associated with all alleles are exactly equal to $\bar{s}$, then we get $\bar{w} = (1 - 0.00376)^{2000} = 0.000535$. This is close to the actual value of $\bar{w}_g$ for $\phi = 1$, which is ~0.000527.

Additional details of the data obtained from the simulations that used the standard parameter values are provided in the first 12 rows of Table 1. For example, the table shows that, with the standard parameter values in effect, the coefficient of variation of w_k values is between 13% and 19%. This range of values is biologically plausible, as it suggests that the variation in fitness between individuals within the population is not extremely large, and of the same order as figures calculated for Drosophila populations (CHARLESWORTH 1987).

Table 1 also shows that, with the standard parameter values in force, only a few different alleles were usually present at any given site. Further analysis suggested that, for most sites, a single allele was present in more

than 85% of the 200 instances of the site within the population [except in the case of obligate asexuality ($\phi = 0$) where the typical figure was closer to 50%]. Furthermore, in all cases except for $\phi = 0$, analysis suggested that the selection coefficient associated with the most common allele at a site was typically about half the size of the average selection coefficient associated with the other alleles at the same site. Thus, we have a picture of a population in which most sites have one or two common alleles, and possibly a few less common alleles that often have larger selection coefficients than the coefficients associated with the most common alleles.

A more complete picture of the effects of ϕ upon selection coefficients can be obtained by examination of Figure 4. This shows the distribution of selection coefficients for $\phi = 0$, $\phi = 0.2$ and $\phi = 1$. The data were collected from generation 100,000 on the second of the two trials run for each of these three values of ϕ (with the standard parameter values in force). The lefthand three panels of the figure suggest that the proportion of selection coefficients in the left-most "bin" ($0 \leq s < 0.01$) is highest for the sexual population ($\phi = 1$). This proportion is somewhat reduced when $\phi = 0.2$, and under asexuality ($\phi = 0$) the proportion is very much reduced, so that the left-most bin does not even contain the majority of selection coefficients, as it does in the $\phi = 0.2$ and the $\phi = 1$ cases. The righthand three panels show the distribution of selection coefficients within the top bin (*i.e.*, these panels show the distribution of selection coefficients in the range $0 \leq s < 0.01$). Note that, in the sexual case ($\phi = 1$) there is a trend such that alleles with lower selection coefficients are more common among top-bin alleles. A similar, but less pronounced trend is present in the $\phi = 0.2$ case. However, this trend appears to be absent in the $0 \leq s < 0.01$ range in the asexual case.

The effects of altering the population size (N): The size of a population is one of the most fundamental determinants of the outcome of evolutionary processes. This is particularly true for processes that depend on the random fixation of genetic elements (CROW and KIMURA 1970). To study how population size affects $\bar{w}_g$ and the other population statistics, we set $\phi = 1$ (obligate sexuality) and imposed four different values of N. These were $N = 50$, $N = 100$, $N = 200$ and $N = 400$.

Figure 5A shows how $\bar{w}_g$ responds to changes in N when $\phi = 1$. Examination of Figure 5A suggests that fitness increases monotonically with N (see also Table 1). This relationship is to be expected, as one-locus theory predicts that deleterious mutations with relatively large selection coefficients will become fixed (or nearly fixed) more readily in small populations than in large ones. This simple interpretation of the results is supported by an examination of Table 1, which shows that, when $\phi = 1$, the average selection coefficient ($\bar{s}$) increases as N decreases.

How do changes in N alter the response of $\bar{w}_g$ to changes in ϕ? To address this question, we must first deal with a problem of data presentation. As we can see from Figure 5A and Table 1, the value of N can have a very strong effect on $\bar{w}_g$ when $\phi = 1$. Indeed, as N changes from $N = 50$ to $N = 400$, the value of $\bar{w}_g$ when $\phi = 1$ changes by more than four orders of magnitude. This makes it difficult to plot all of the data on a single graph in a useful way unless some transformation is used. We decided to normalize the data by dividing the $\bar{w}_g$ values obtained for each pair of ϕ and N values by the average of the two $\bar{w}_g$ values obtained for the same value of N, and with $\phi = 1$. Thus, all of the averaged and normalized $\bar{w}_g$ values will be equal to 1.0 for $\phi = 1.0$. The remaining normalized data points allow comparison of the way that the $\bar{w}_g$ values respond to changes in ϕ for different values of N. This procedure will be used repeatedly in this paper, and it will be referred to as the standard normalization procedure. The standard normalization procedure does not change the shape of a curve when it is applied, but it does ensure that the curve gives a values of 1.0 when $\phi = 1$.

The standard normalization procedure was used to produce the data for Figure 5B. The four curves that appear in Figure 5B connect the normalized $\bar{w}_g$ values that were obtained for the four values of N. The shapes of each of these curves would be exactly the same if the standard normalization procedure had not been applied. That is to say, the ratio of any two normalized $\bar{w}_g$ values that are connected by one of the curves in Figure 5B would have been exactly the same if we had plotted the $\bar{w}_g$ data without normalization.

Examination of Figure 5B reveals that the curves for the larger values of N rise more gently toward 1.0 as ϕ increases. For example, the points for $N = 400$ are always the highest on the graph for any given value of ϕ (as long as $\phi < 1$) and the points for $N = 50$ are always the lowest. This suggests that increasing ϕ is likely to increase the value of $\bar{w}_g$ more (in percentage terms) when N is small, as compared to the case where N is large. In the limit as N goes to infinity, it may well be that changing ϕ will have no effect on fitness at all. Although it is not apparent from the figure, the differentiation of the normalized fitnesses becomes greater as ϕ becomes smaller. Thus, for example, the normalized fitness for the $N = 400$ case divided by the normalized fitness for the $N = 100$ case is equal to 1.37 when $\phi = 0.8$, but it increases to 41.6 when $\phi = 0.2$. When $\phi = 0$, the ratio is much larger, at 66,263. Note that a similar accentuation of differences as ϕ declines characterizes most of the other comparisons of normalized fitnesses that will be described in the next three sections (which describe the effects of manipulating L, U and $|m|$). However, it seems that no such simple pattern characterizes the results on recombination rate, which follows the sections on L, U and $|m|$.

Next, let us consider the effect of ϕ on fitness after

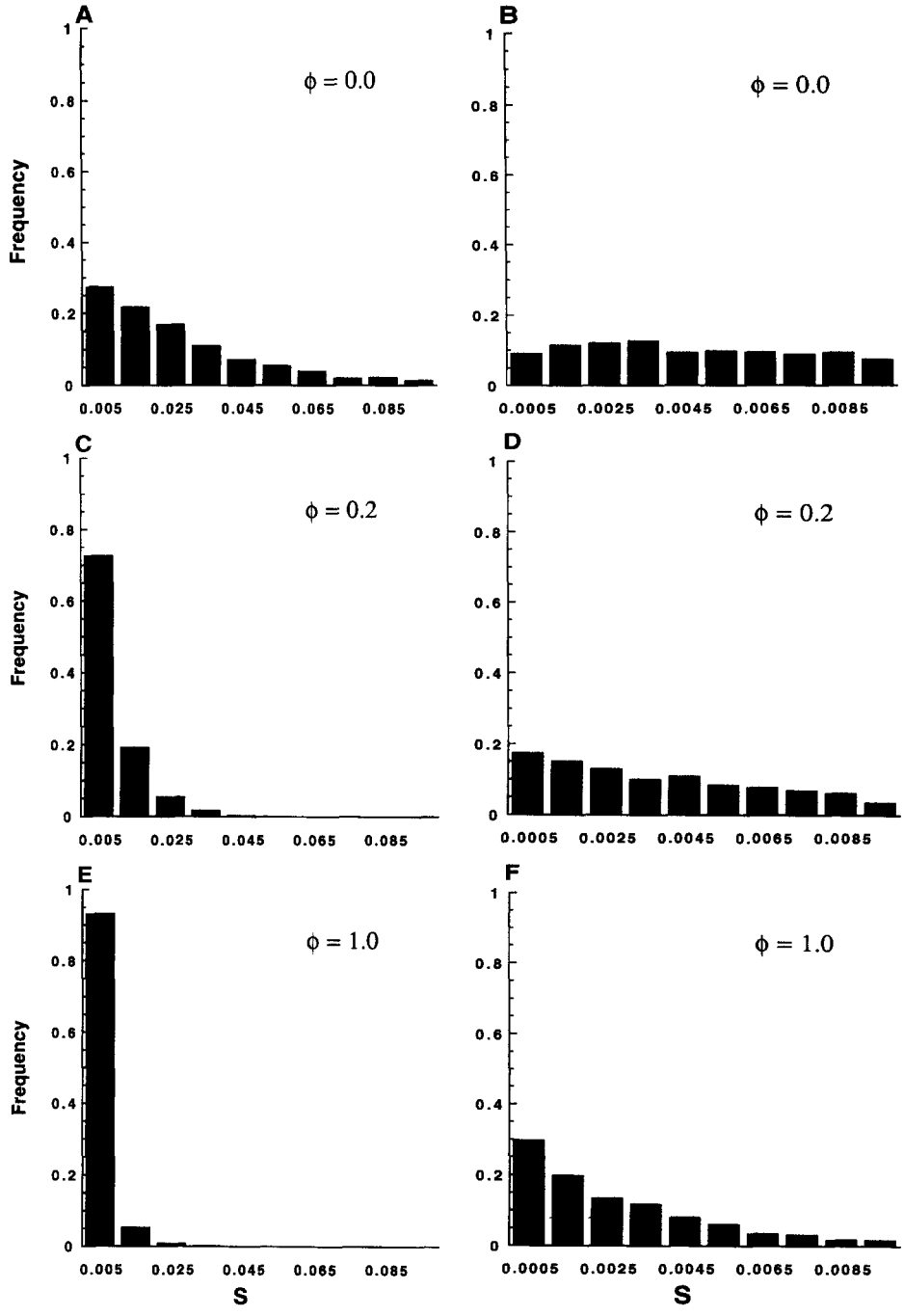

FIGURE 4.—The distribution of selection coefficients when the standard parameter values were in force for $\phi = 0$, $\phi = 0.2$ and $\phi = 1$. The values given on the abscissas are the center points for each of the "bins." Thus, for example, the left-most bar in each of the lefthand three panels gives the frequency of selection coefficients that satisfy $0 \leq s < 0.01$. The next bar is for selection coefficients that satisfy $0.01 \leq s < 0.02$, and so forth. The panels on the righthand give the distribution of selection coefficients in the range $0 \leq s < 0.01$ (*i.e.*, these panels give a detailed view of the selection coefficients that lie within the left-most bin in the lefthand panels). In all cases, the frequencies have been normalized so that the sum of the frequencies for all 10 bins sums to 1.0. However, in the case of the lefthand three panels normalization produces no perceptible change in the height of the bars. This is because the absolute frequency of alleles with associated selection coefficients in excess of 0.1 is only 0.0296, 0.000355 and 0.000185 for $\phi = 0$, $\phi = 0.2$ and $\phi = 1$, respectively.

correction for the cost of sex (*i.e.*, on the $\bar{w}_{gc}$ values). The relevant data were subjected to the standard normalization procedure, and then they were plotted as shown in Figure 5C. Note that the plotted normalized $\bar{w}_{gc}$ values are monotonically increasing in all cases, except where $N = 400$. With this relatively large value of N, the $\bar{w}_g$ values are monotonically increasing, but for high values of ϕ the increase is too gentle to allow an

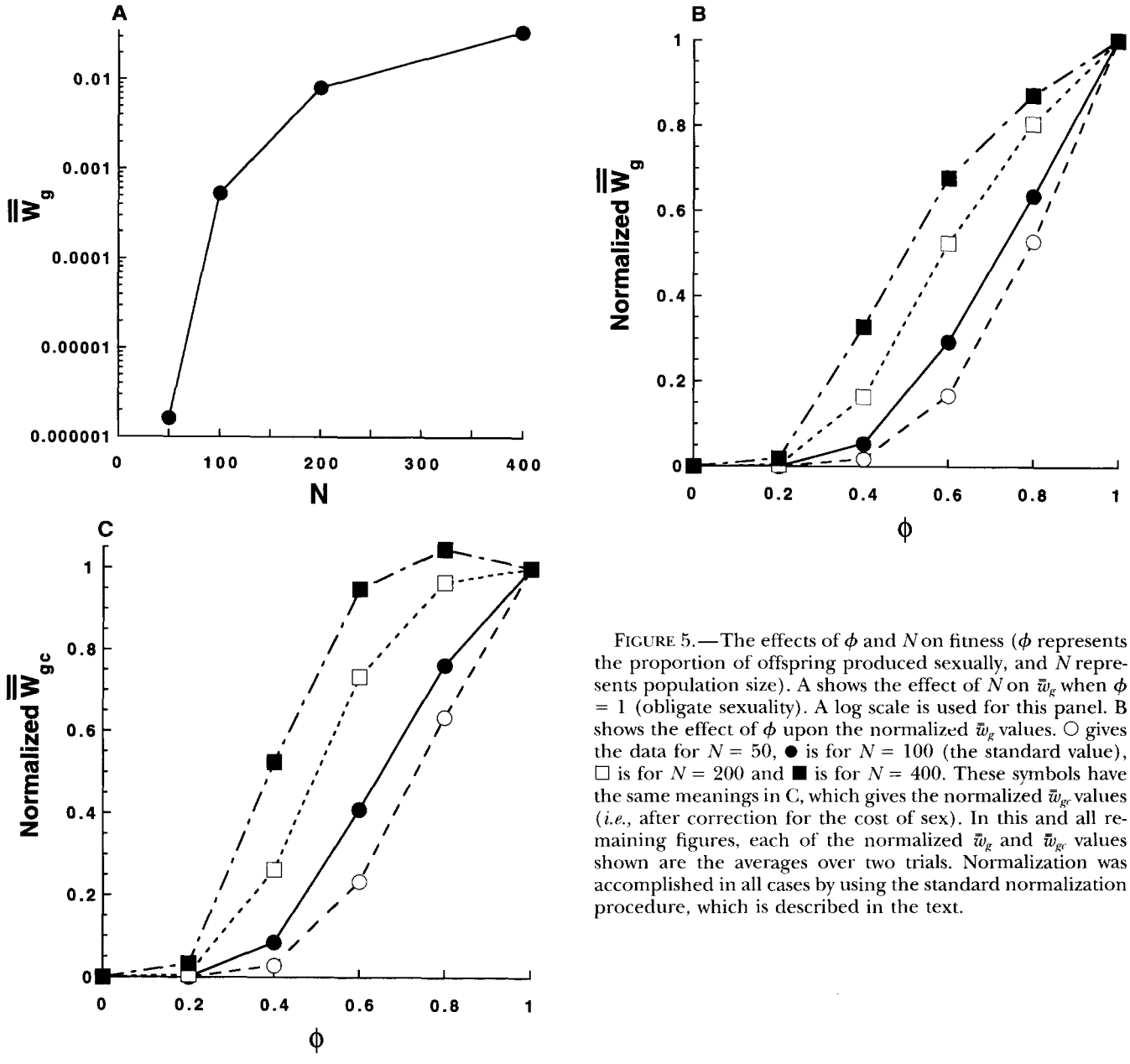

FIGURE 5.—The effects of ϕ and N on fitness (ϕ represents the proportion of offspring produced sexually, and N represents population size). A shows the effect of N on $\bar{w}_g$ when $\phi = 1$ (obligate sexuality). A log scale is used for this panel. B shows the effect of ϕ upon the normalized $\bar{w}_g$ values. ○ gives the data for $N = 50$, ● is for $N = 100$ (the standard value), □ is for $N = 200$ and ■ is for $N = 400$. These symbols have the same meanings in C, which gives the normalized $\bar{w}_{gc}$ values (*i.e.*, after correction for the cost of sex). In this and all remaining figures, each of the normalized $\bar{w}_g$ and $\bar{w}_{gc}$ values shown are the averages over two trials. Normalization was accomplished in all cases by using the standard normalization procedure, which is described in the text.

increase in the $\bar{w}_{gc}$ values. Instead, when $N = 400$ and when the other parameters take their standard values, it appears that a species for which most, but not all, of the offspring are produced sexually ($\phi \approx 0.8$) will win any ecological competition. With the smaller values of N (*i.e.*, $N = 50$, $N = 100$ and $N = 200$) it appears that obligate sex ($\phi = 1$) is favored.

The effects of altering the number of sites (L): What effect does the number of sites undergoing selection have on evolutionary outcomes? To answer this question, we turned once again to a computer simulation study.

It is well appreciated that the genomic rate of mutation (U) is an important determinant of the outcome of evolution (MULLER 1964; KONDRASHOV 1988; BULMER 1989; BÜRGER *et al.* 1989; CHARLESWORTH 1990; CHARLESWORTH *et al.* 1993; PECK 1994). This observation will be confirmed in the context of the present model in the next section. The effect of U on evolutionary outcomes means that, if we are to understand the effect of the number of sites (L), then it is important to keep U constant while changing L. This means changing μ, the allelic rate of mutation. In our study, we set the genomic rate of mutation to its standard value of $U = 2.0$, and let L take on the values $L = 240$, $L = 500$, $L = 1000$, $L = 2000$. With $U = 2.0$, these values of L correspond to allelic mutation rates of $\mu = 0.00417$, $\mu = 0.002$, $\mu = 0.001$ and $\mu = 0.0005$, respectively. The standard number of generations (100,000) was used for all of these trials, except in the case of $L = 2000$. Here, the low allelic mutation rate means that it takes substantially longer to establish a stationary distribution, and

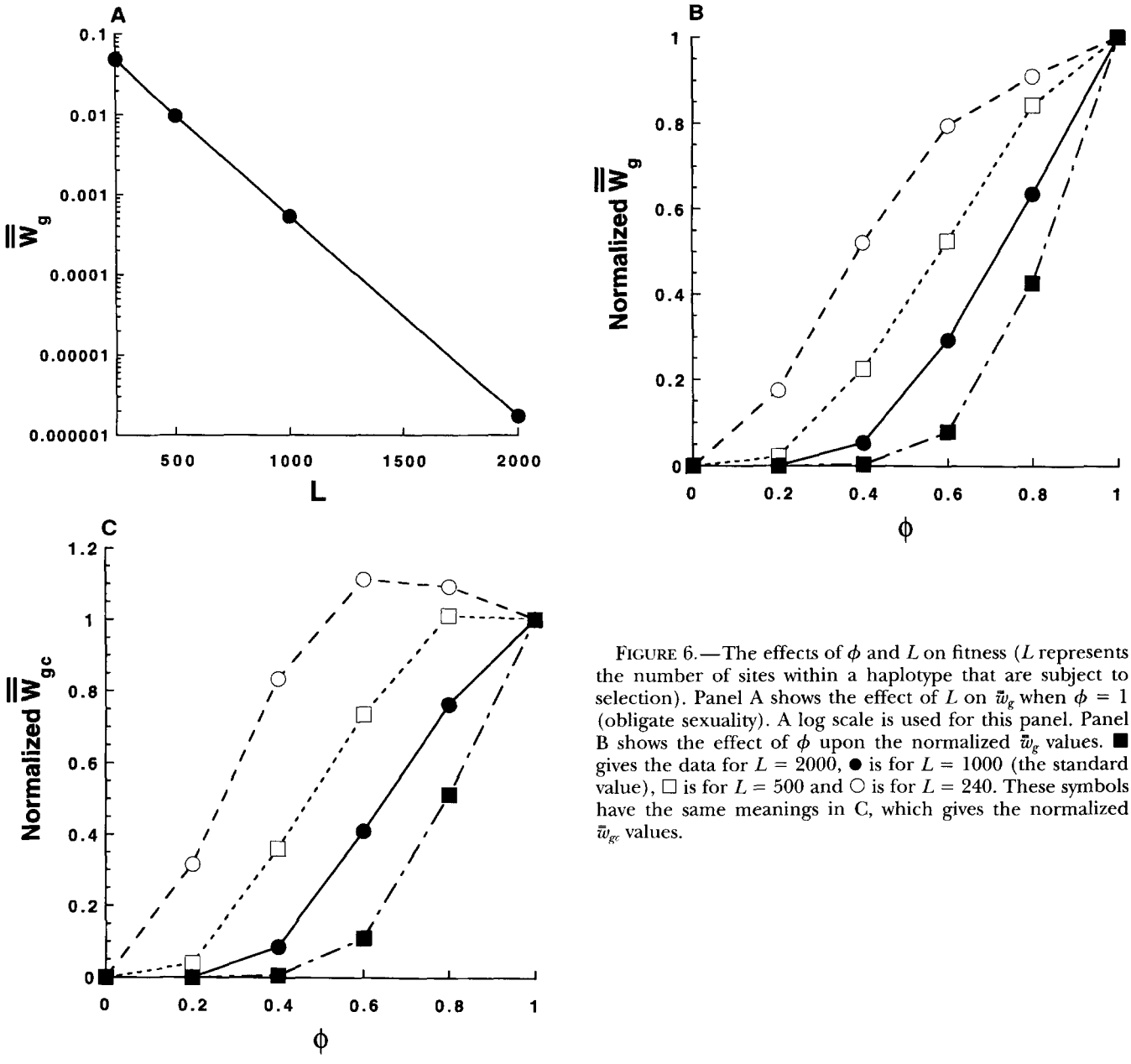

FIGURE 6.—The effects of ϕ and L on fitness (L represents the number of sites within a haplotype that are subject to selection). Panel A shows the effect of L on $\bar{w}_g$ when $\phi = 1$ (obligate sexuality). A log scale is used for this panel. Panel B shows the effect of ϕ upon the normalized $\bar{w}_g$ values. ■ gives the data for $L = 2000$, ● is for $L = 1000$ (the standard value), □ is for $L = 500$ and ○ is for $L = 240$. These symbols have the same meanings in C, which gives the normalized $\bar{w}_{gc}$ values.

so we ran the $L = 2000$ trials for 150,000 generations, instead of the standard 100,000 generations. We collected the data for the output statistics during the last 50,000 generations, as usual.

The change in $\bar{w}_g$ as a function of L is illustrated in Figure 6A. All of the data shown in Figure 6A were collected with $\phi = 1$. As Figure 6A shows, $\bar{w}_g$ falls dramatically as L increases. Table 1 shows that the increase in L does not have much of an effect on $\bar{V}_w$. However, $\bar{s}$ and the average number of segregating alleles per site decrease as L increases. Note that the decrease in $\bar{s}$ as L increases is insufficient in magnitude to reverse the inverse relation between L and $\bar{w}_g$, which is seen in Figure 6A.

In Figure 6B we can see how changes in L affect the response of $\bar{w}_g$ to changes in ϕ. The values plotted in Figure 6B are the $\bar{w}_g$ values after application of the standard normalization procedure. Figure 6B shows that, as L increases, $\bar{w}_g$ rises more sharply with ϕ. Thus, it appears that obligate sexuality is more likely to be favored when the number of sites under selection is relatively large. Figure 6C lends further support to this idea, as it shows the same data after correction for the cost of sex (the $\bar{w}_{gc}$ values). Figure 6C shows that, for the values of L tested, it appears that obligate sex is favored when $L \geq 1000$. For $L = 500$ the $\bar{w}_{gc}$ values are nearly equal for $\phi = 0.8$ and $\phi = 1$. For $L = 240$, it appears that a species with $\phi \approx 0.6$ would be favored in a competition with species with a species that produced substantially more or substantially less of its offspring by means of sexual reproduction.

The effects of altering the genomic rate of muta-

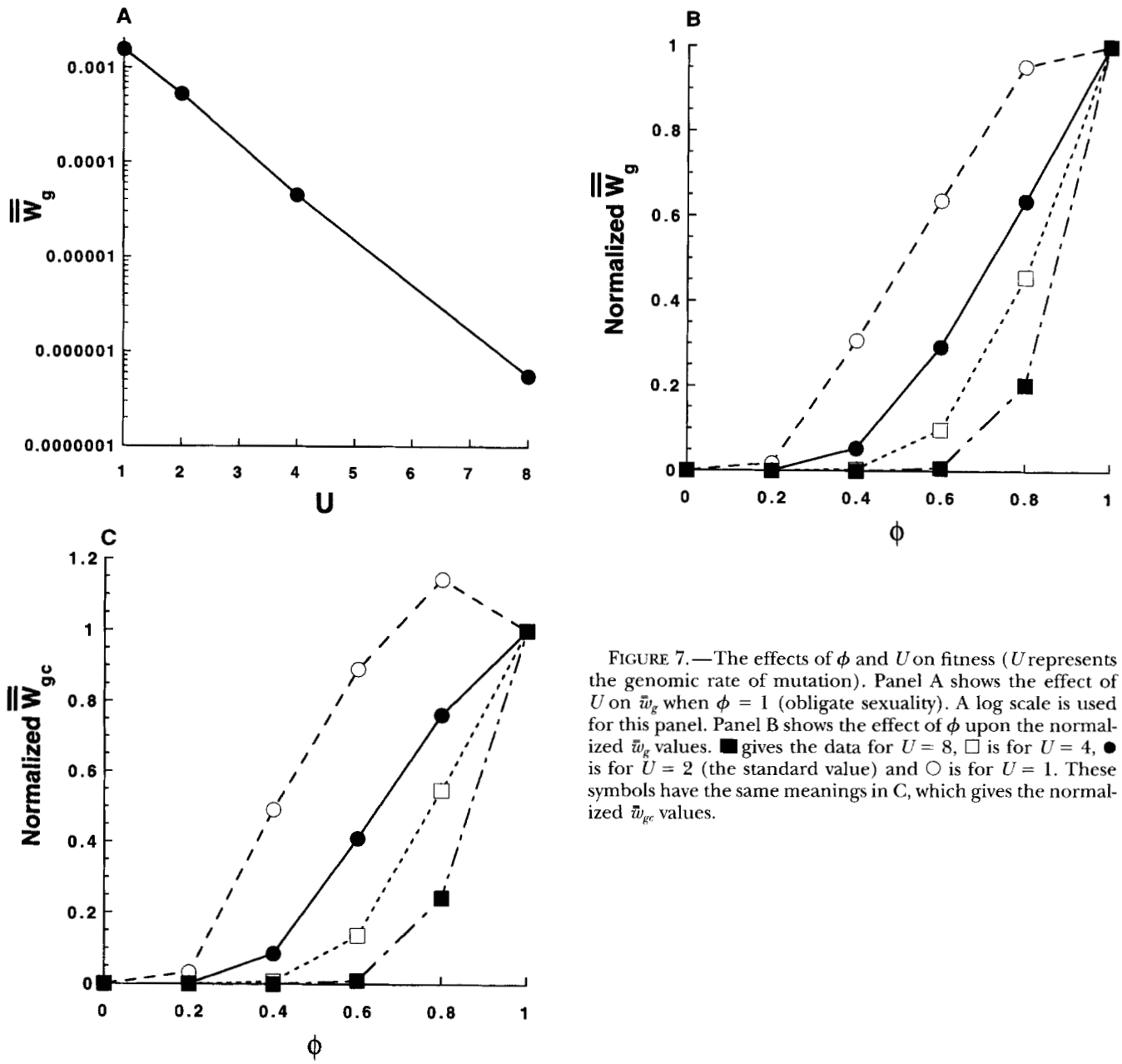

FIGURE 7.—The effects of ϕ and U on fitness (U represents the genomic rate of mutation). Panel A shows the effect of U on $\bar{w}_g$ when $\phi = 1$ (obligate sexuality). A log scale is used for this panel. Panel B shows the effect of ϕ upon the normalized $\bar{w}_g$ values. ■ gives the data for $U = 8$, □ is for $U = 4$, ● is for $U = 2$ (the standard value) and ○ is for $U = 1$. These symbols have the same meanings in C, which gives the normalized $\bar{w}_{gc}$ values.

tion (U): Our next simulation study examined the effect of the genomic rate of mutation upon $\bar{w}_g$. Four values of U were tested, and these were $U = 1.0$, $U = 2.0$, $U = 4.0$ and $U = 8.0$. The standard value of L was used in these simulations ($L = 1000$), and this means that these four values of U correspond to allelic mutation rates of $\mu = 0.0005$, $\mu = 0.001$, $\mu = 0.002$ and $\mu = 0.004$, respectively. With low mutation rates it takes longer for all the $x = 0$ alleles to be eliminated from the population and for an apparent stationary distribution to be established. With this in mind, we ran the $U = 1.0$ trials for 100,000 generations before we began the 50,000 generations during which the output statistics were calculated (thus, these trials ran for 150,000 generations, instead of the usual 100,000 generations).

Figure 7A shows how changing U affects $\bar{w}_g$ when $\phi = 1$. As can be seen from Figure 7A, $\bar{w}_g$ undergoes a considerable decline as U rises from $U = 1.0$ to $U = 8.0$. Examination of Table 1 suggests that $\bar{s}$ increases as U increases when $\phi = 1$. The decrease in fitness caused by higher U values is apparently caused, in part, by a decrease in the quality of common alleles. Note also from Table 1 that $\bar{V}_w$ increases as U rises. This result is in line with intuition (more variation in fitness is to be expected as the mutation rate rises). It may also help to explain the effects of U on $\bar{w}_g$. This idea will be explored further in the discussion section.

Figure 7B shows how the genomic rate of mutation affects the response of $\bar{w}_g$ to different values of ϕ. As can be seen from Figure 7B, $\bar{w}_g$ seems to rise more sharply with ϕ when U is relatively high, as compared to the cases where U is relatively low. This same pattern is reflected in

Figure 7C, which shows the $\bar{w}_{gc}$ values after application of the standard normalization procedure. Examination of Figure 7C suggests that, when the parameters except for U are set to their standard values, obligate (or near obligate) sexuality will be favored in between-species contests if $U \geq 2$, but not when $U \leq 1$.

The effects of altering the average effect of mutations ($|m|$): Next, let us consider what happens to $\bar{w}_g$ when we change the value of $|m|$. As stated above, our standard value of $|m|$ is 0.0206, and this means that mutations to perfect alleles (for which $x = 0$) will lead to the imposition of a selection coefficient with an average value of $s = 0.02$. In addition to the standard value of $|m|$, we considered four other values of $|m|$, and these were $|m| = 0.00201$, $|m| = 0.0102$, $|m| = 0.0425$, and $|m| = 0.281$. When applied to perfect alleles, these values of $|m|$ lead to average selection coefficients of $s = 0.002$, $s = 0.01$, $s = 0.04$, and $s = 0.2$, respectively. We found that the loss of all the $x = 0$ alleles and the establishment of an apparent stationary distribution takes substantially longer for the $|m| = 0.281$ case, as compared to the other cases. This is not surprising, since it is reasonable to expect that a large value of $|m|$ will lead to fewer mutations that are effectively neutral. With this in mind, we ran the $|m| = 0.281$ trials for 200,000 generations before starting the 50,000 generations during which the output statistics were calculated (thus, the $|m| = 0.281$ trials ran for a total of 250,000 generations).

Figure 8A shows how changing $|m|$ affects $\bar{w}_g$ when $\phi = 1$. Figure 8A suggests that $\bar{w}_g$ tends to fall as $|m|$ rises. Table 1 shows that, as $|m|$ rises, there are substantial increases in $\bar{s}$ and $\bar{V}_w$. Thus, raising the value of $|m|$ increases the average selection coefficient and the normalized variation in fitness.

Figure 8B shows how the value of $|m|$ affects the response of $\bar{w}_g$ to different values of ϕ. Figure 8B shows that $\bar{w}_g$ tends to rises more sharply with ϕ when $|m|$ is relatively high, as compared to the cases where $|m|$ is relatively low. Figure 8C shows the same data after correction for the cost of sex (*i.e.*, it shows the $\bar{w}_{gc}$ values). Examination of Figure 8C suggests that, when the parameters except for $|m|$ are set to their standard values, obligate (or near obligate) sexuality will be favored in between-species contests if $|m| \geq 0.0206$. When $|m| = 0.00201$, it appears that a species for which $\phi \approx 0.6$ would be favored, whereas, when $|m| = 0.0102$, it appears that species with $\phi \approx 0.8$ would be favored.

The effects of altering the rate of recombination (r): No recombination occurs when individuals are produced asexually. Thus, we might expect that changes in the between-site rate of recombination (r) would have an effect that is similar to the effect of changing the value of ϕ. Figure 9A confirms that this is the case. All of the points for Figure 9A were calculated with the standard parameter values, except that values of r ranging from 0.0 to 0.5 were used. The value of ϕ was set to 1.0 for the collection of all the data points shown in Figure 9A. As can be seen from Figure 9A, $\bar{w}_g$ rises very sharply as r increases toward the standard value of $r = 0.016$. However, it appears that very little additional increase in $\bar{w}_g$ can be achieved by raising r beyond the standard value. Note that the highest value of r tested ($r = 0.5$) is biologically unrealistic for a model in which there are 1000 sites. It was included to see what happens in the limit as linkage becomes loose. Table 1 shows that the values of $\bar{s}$ also follow the expected pattern, with the smallest values for the highest rates of recombination. However, the difference in $\bar{s}$ values between the $r = 0.016$ case and the $r = 0.5$ case is very slight.

What effect does the rate of recombination have on the way that $\bar{w}_g$ responds to changes in ϕ? To answer this question, we ran simulations using six values of ϕ and four different values of r. The r values were $r = 0$, $r = 0.0002$, $r = 0.016$ (the standard value) and $r = 0.5$. The data were normalized using the standard normalizing procedure, and they are plotted in Figure 9B. Note that $\bar{w}_g$ appears to be a monotonically increasing function of ϕ regardless of the value of r. However, there is no apparent monotonic relationship between r and the effectiveness of increasing ϕ as a way of enhancing fitness. For example, the figure shows that, when $\phi \geq 0.6$, increasing ϕ seems to be least effective when $r = 0$ (the lowest value of r considered) and most effective when $r = 0.0002$, which is the next-to-lowest value of r studied. The plots for the highest values of r considered ($r = 0.016$ and $r = 0.5$) lie between those for the lowest values considered.

Figure 9C shows the $\bar{w}_{gc}$ points corresponding to the points that appear in Figure 9B. The data for Figure 9C were normalized using the standard normalization procedure. The figure suggests that, when $r = 0$ and the other parameters are set to their standard values, a species for which $\phi = 0.8$ will be a better competitor than an obligately sexual species ($\phi = 1$) after the cost of sex is taken into account. For all other values of r considered, an obligately sexual species appears to be the best competitor.

SYNERGISTIC EPISTASIS

Thus far, we have considered a strictly multiplicative model. The multiplicative model is conceptually convenient because a given allele will have the same effect on fitness (in percentage terms) without regard to the rest of the genome in which it occurs. Although the multiplicative model is convenient, it may also be biologically unrealistic. An alternative to the multiplicative model is a model that incorporates synergistic epistasis. Under synergistic epistasis, deleterious mutations have a smaller detrimental effect (in percentage terms) in high-fitness genomes than in low-fitness genomes.

There are a variety of reasons to think that a model that incorporates some sort of synergistic epistasis is more realistic than a multiplicative model (CROW 1970;

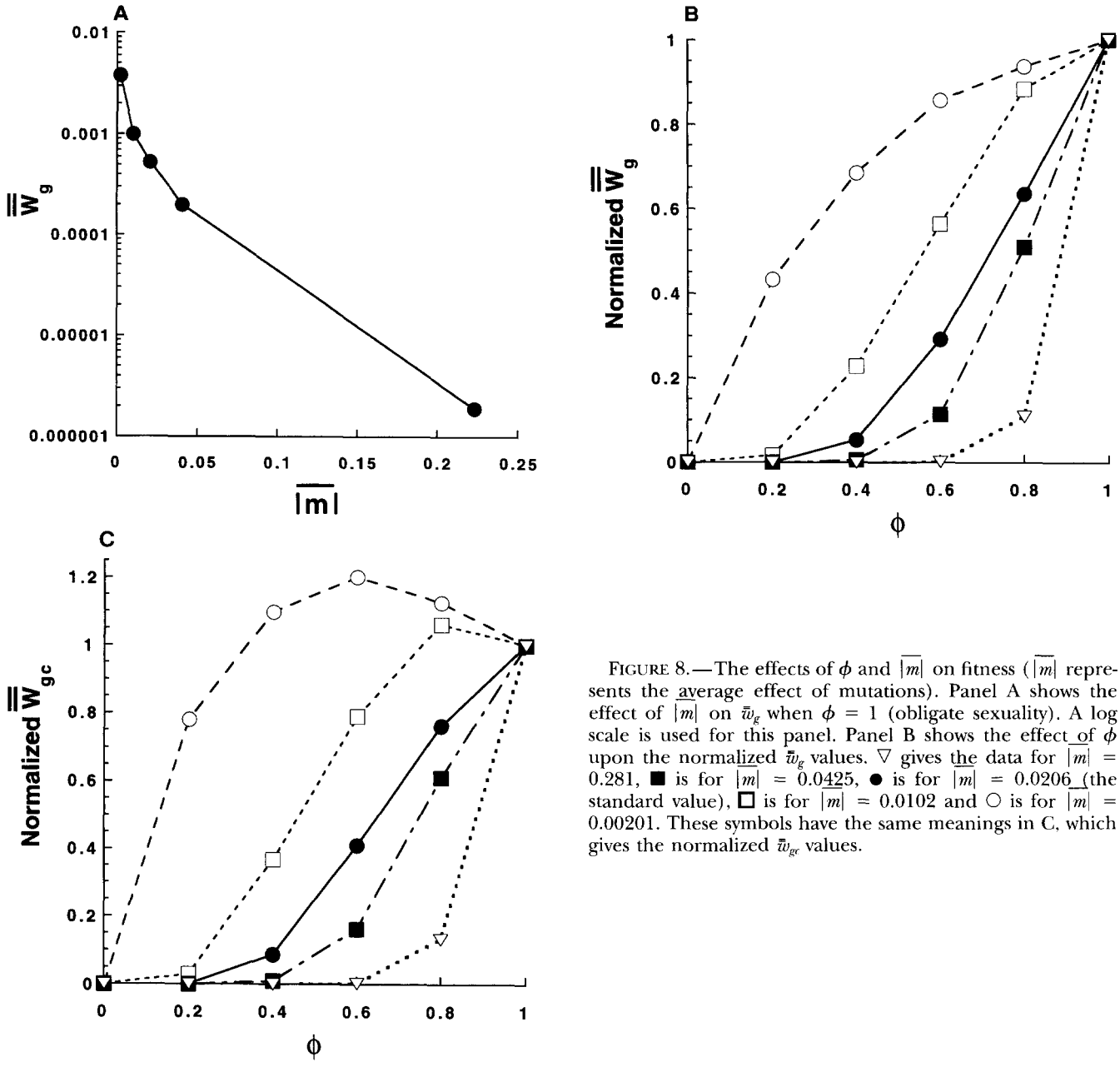

FIGURE 8.—The effects of ϕ and $\overline{|m|}$ on fitness ($\overline{|m|}$ represents the average effect of mutations). Panel A shows the effect of $|m|$ on $\bar{w}_g$ when $\phi = 1$ (obligate sexuality). A log scale is used for this panel. Panel B shows the effect of ϕ upon the normalized $\bar{w}_g$ values. ▽ gives the data for $|m| = 0.281$, ■ is for $|m| = 0.0425$, ● is for $|m| = 0.0206$ (the standard value), □ is for $|m| = 0.0102$ and ○ is for $|m| = 0.00201$. These symbols have the same meanings in C, which gives the normalized $\bar{w}_{gc}$ values.

KONDRASHOV 1988; SZATHMÁRY 1993; KONDRASHOV 1995; DE VISSER *et al.* 1996; HURST and PECK 1996). We will not attempt to provide an in-depth review of the literature on synergistic epistasis here, but it may be worth noting several arguments in favor of the view that this sort of epistasis is common. First, there appears to be quite a bit of redundancy in the genome, with multiple genes fulfilling similar functions (TAUTZ 1992; THOMAS 1993). It seems reasonable to expect that fitness would not decrease by much if the function of one of several genes capable of fulfilling a given function was rendered inoperative or less efficient by a mutation. However, if the genome was highly degraded so that only one of the several genes that fulfil a given function is operational, then mutations of that gene might have a very large effect on fitness.

A second reason to expect synergistic epistasis has to do with the idea of an enzymatic "law of diminishing returns" such that, as a particular enzyme becomes more efficient, further enhancements in efficiency have a smaller effect on flux through the biochemical pathway, and thus, they may produce smaller improvements in fitness (SZATHMÁRY 1993). Similar arguments can be formulated to support the idea of synergistic epistasis for genes that do not code for enzymes, and for noncoding regions that are under selection.

A final argument in favor of the idea of synergistic epistasis has to do with genetic load. A common definition of genetic load (G) that appears in CROW and KIMURA's text (1970) is

$$G = \frac{w_{max} - \bar{w}}{w_{max}}, \qquad (10)$$

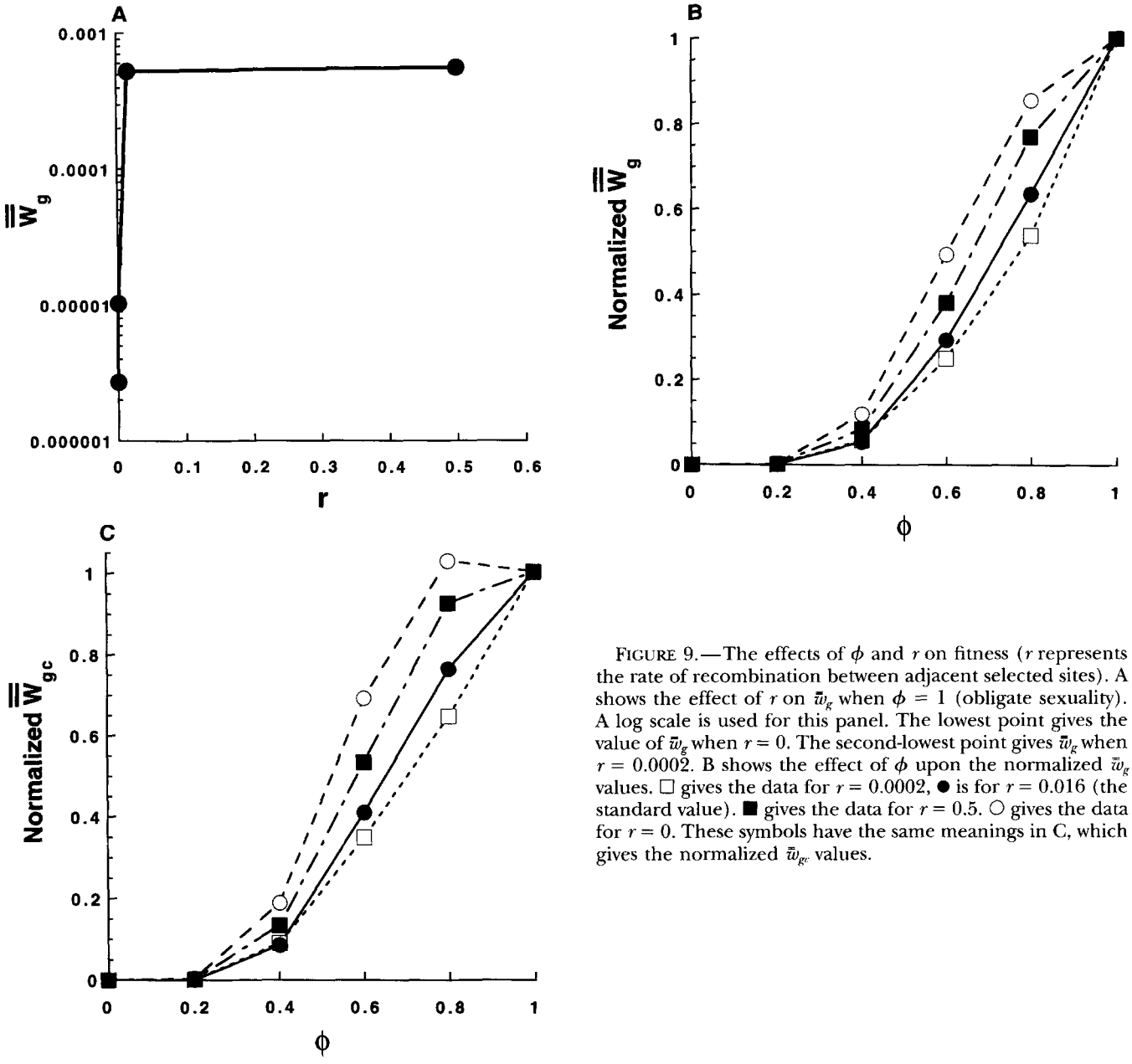

FIGURE 9.—The effects of ϕ and r on fitness (r represents the rate of recombination between adjacent selected sites). A shows the effect of r on $\bar{w}_g$ when $\phi = 1$ (obligate sexuality). A log scale is used for this panel. The lowest point gives the value of $\bar{w}_g$ when $r = 0$. The second-lowest point gives $\bar{w}_g$ when $r = 0.0002$. B shows the effect of ϕ upon the normalized $\bar{w}_g$ values. □ gives the data for $r = 0.0002$, ● is for $r = 0.016$ (the standard value). ■ gives the data for $r = 0.5$. ○ gives the data for $r = 0$. These symbols have the same meanings in C, which gives the normalized $\bar{w}_{gc}$ values.

where w_{max} is the maximum possible value of $\bar{w}$. Thus, we have $0 \leq G \leq 1$. In the case of the models under study here we have $w_{max} = 1$, and so $G = 1 - \bar{w}$. Immediately we can see from Equation 10 (and from Table 1) that, under the multiplicative model that we have considered thus far, genetic load is close to its maximum value of 1.0, at least for the parameter values considered above. Examination of Table 1 also suggests that genetic load can be lowered to a reasonable level by, for example, decreasing the number of loci, or by increasing the population size. The first of these changes would make the model less biologically realistic, but the latter change would make it more so (very few populations of interest have only a few hundred members). Nevertheless, it is not at all clear that biologically reasonable population sizes would lower load substantially if the number of sites under selection was simultaneously increased to a reasonable level.

It is well known that synergistic epistasis can reduce the level of genetic load experienced by a population (KIMURA and MARUYAMA 1966). This observation provides our third and final motivation for studying a model that incorporates synergistic epistasis. Some researchers believe that a high level of genetic load is no reason to dismiss a model as unreasonable (*e.g.*, GILLESPIE 1991). We do not wish to take a position on this contentious issue, but we do believe that it is worth demonstrating that load can be substantially reduced by introducing synergistic epistasis. This is the central purpose of the present section.

A modified model: The multiplicative model considered thus far is equivalent to an exponential model, as

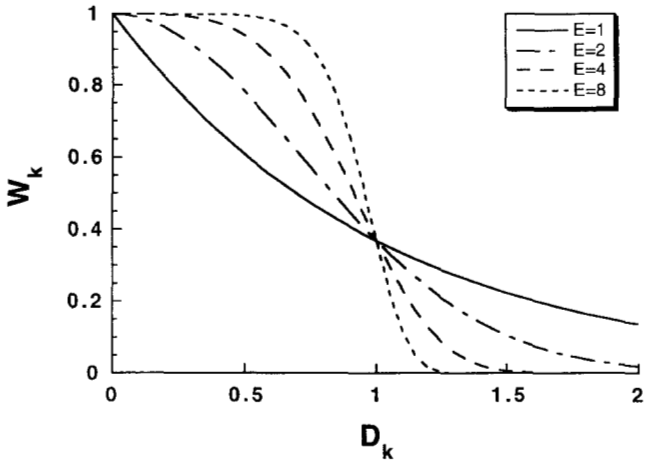

FIGURE 10.—The curves that relate the value of D_k to the value of w_k for various values of E (the epistasis parameter). Note that, when $E = 1$, we have the strictly multiplicative (*i.e.*, nonepistatic) model.

shown by Equations 1 and 2. To introduce synergistic epistasis, we modify the multiplicative model by generalizing Equation 2 to read as follows:

$$w_k = \exp(-D_k^E). \tag{11}$$

Recall that D_k is a measure of the distance from the optimal genotype for adult k. The variable E is the epistasis parameter, and when $E = 1$, Equation 11 is equivalent to Equation 2, and the model is strictly multiplicative (*i.e.*, no synergistic epistasis). When $E > 1$, synergistic epistasis is in force. Under synergistic epistasis, mutations tend to have a smaller effect than in the strictly multiplicative case so long as D_k is small. However, when $D_k \geq 1$, mutations have a greater effect than in the strictly multiplicative case, and the magnitude of the fitness effects (in percentage terms) of a deleterious mutation increases with D_k. In particular, we have

$$\frac{(\partial w_k/\partial D_k)}{w_k} = -ED_k^{E-1} \tag{12}$$

Results: Synergistic epistasis introduces some complicated effects, and we will not attempt a complete analysis here. Rather, we will restrict ourselves largely to a simple demonstration that synergistic epistasis can ameliorate the load problem.

For the purposes of this simple demonstration, we chose four different levels of E. These were $E = 1$, $E = 2$, $E = 4$ and $E = 8$. Figure 10 shows the shape of the curves that relate the value of D to fertility (w_k) for each of these values of E. Note that $E = 1$ is identical to the multiplicative model that was addressed in the foregoing sections.

Table 1 shows some of the values of $\bar{w}_g$ achieved when all the parameters took their standard values, and when the value of E was varied. The symbol N/A appears in the $\bar{s}$ column of Table 1 for those cases where $E > 1$. This is because, when $E > 1$, the selection coefficient associated with a particular allele depends on the rest of the genotype in which it occurs. Thus, $\bar{s}$ is not well defined when $E > 1$.

Table 1 and Figure 11A show that, as E increases, so does $\bar{w}_g$ for sexual populations. This is in accord with previously published results (KIMURA and MARUYAMA 1966). For $\phi = 1$ and $E = 8$, we have $\bar{w}_g \approx 0.139$, which seems like a very reasonable level of fitness, in that the fittest-possible individual is only about seven times more fertile than the average member of this population. Data in the table also suggest that, as E increases, so does $\bar{V}_w$. This is not surprising, as the relationship between D and w is very different when $E \gg 1$, as compared to the case where $E = 1$. In addition, examination of the table suggests that when $E > 1$, $\bar{V}_w$ tends to increase as ϕ decreases. This makes sense, as decreases in ϕ tend to increase the level of genetic deterioration (D_k) and when $E > 1$, the relative size of the effect on w_k of a particular FAM increases as D_k increases (see Equation 12).

In Figure 11B, we see the values of $\bar{w}_g$ for various levels of E and ϕ, after application of the standard normalization procedure. There appears to be no clear and monotonic relationship between the value of E and the effectiveness of sexuality as an enhancer of fitness. However, for all the values of E that were examined, $\bar{w}_g$ increased monotonically with ϕ. Furthermore, in all of these cases, the increase in $\bar{w}_g$ with ϕ was sufficiently large to compensate for the cost of sex, and thus, for each value of E, an obligately sexual population ($\phi = 1$) was fitter than the partially sexual or asexual alternatives, even after taking the cost of sex into account (see Figure 11C).

The elevated values of $\bar{V}_w$ for $E > 1$ make comparison with the $E = 1$ results difficult, and they also compromise the biological realism of the model, as such high values of V_w may not be common (CHARLESWORTH 1987). For this reason, we reran the simulations, and we changed the value of $|\bar{m}|$ from its standard value of 0.0206 to a new value of 0.005. When $\phi = 1$ and $E = 2$, this reduces the value of $\bar{V}_w$ to a level that is similar to the levels observed in the nonepistatic model (see Table 1). However, $\bar{V}_w$ still increases as E increases (though the levels remain far below the levels seen when the standard value of $\bar{m}$ was used).

Figure 12A shows the levels of $\bar{w}_g$ obtained with $|\bar{m}| = 0.005$, $\phi = 1$, and with various levels of E. As can be seen from the figure (and from Table 1) increasing the value of E increases mean fitness when $\phi = 1$, just as in the previous case, where $|\bar{m}|$ was equal to 0.0206. The maximum level of fitness observed was achieved with $E = 8$, and this was $\bar{w}_g \approx 0.318$, which is nearly one-third of the maximum-possible level of fitness. Thus, with $E = 8$, load seems to be a nonproblem, at least for sexual populations.

In Figure 12B, we see the values of $\bar{w}_g$ for various levels of E and ϕ, after application of the standard normalization procedure. For each of the values of E stud-

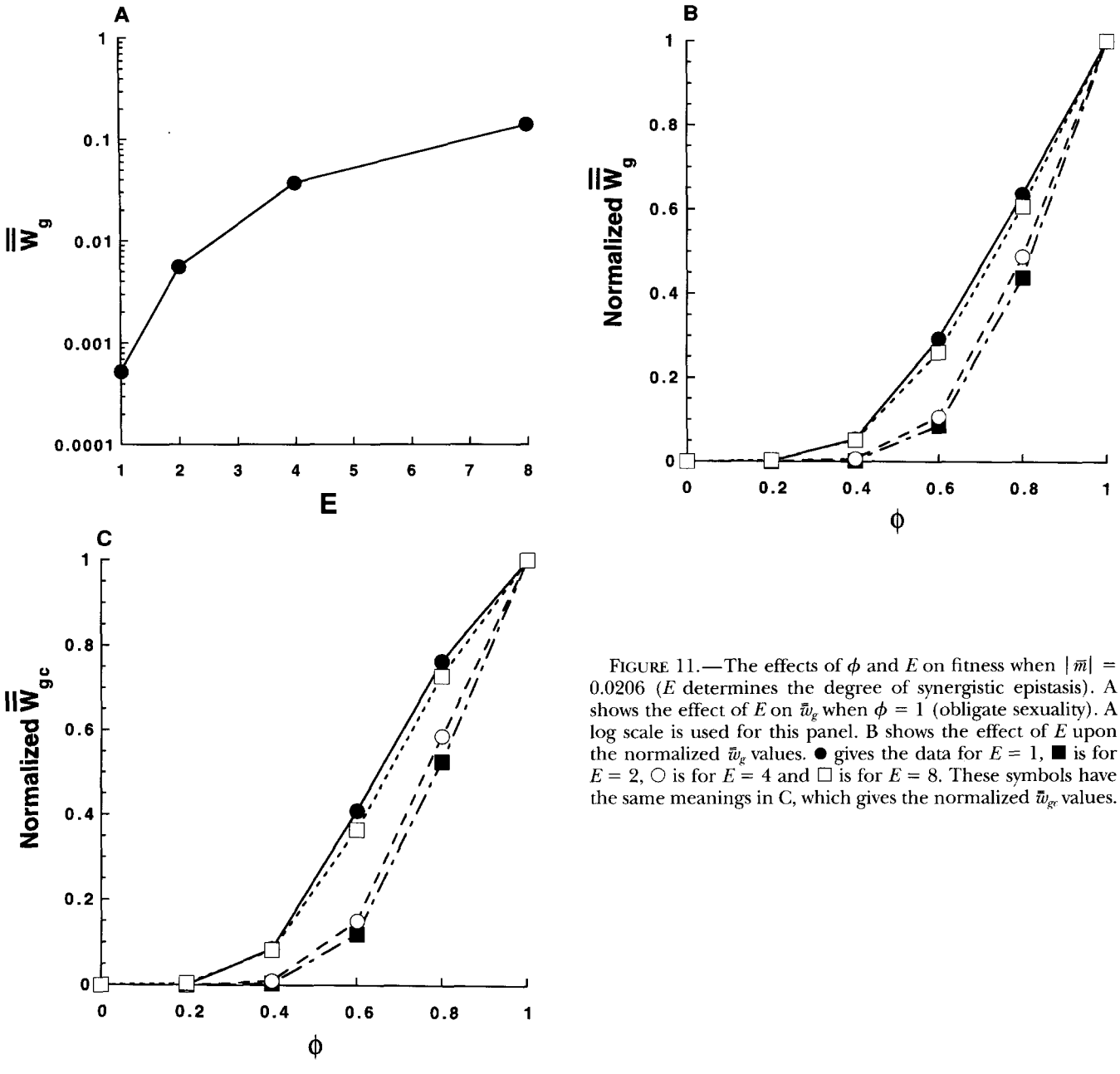

FIGURE 11.—The effects of ϕ and E on fitness when $|\bar{m}| = 0.0206$ (E determines the degree of synergistic epistasis). A shows the effect of E on $\bar{w}_g$ when $\phi = 1$ (obligate sexuality). A log scale is used for this panel. B shows the effect of E upon the normalized $\bar{w}_g$ values. ● gives the data for $E = 1$, ■ is for $E = 2$, ○ is for $E = 4$ and □ is for $E = 8$. These symbols have the same meanings in C, which gives the normalized $\bar{w}_{gc}$ values.

ied, $\bar{w}_g$ rises monotonically with ϕ. Once again, there is no clear and monotonic relationship between E and the effectiveness of sex, although, in general, sex seems to be least effective when $E = 1$, and it is also relatively ineffective when $E = 8$. Sex seems to be more effective as an enhancer of fitness when $E = 2$ and $E = 4$.

Comparison of Figures 11B and 12B suggests that sex is less effective at improving fitness when $|m| = 0.005$, compared to when $|m|$ takes the standard value of 0.0206. This impression is supported by the data shown in Figure 12C, which shows the $\bar{w}_{gc}$ data (after normalization) for the case where $|m| = 0.005$. For this value of $|m|$, $\bar{w}_{gc}$ reaches its maximum when $\phi = 0.8$ in the case where $E = 8$. When $E = 1$, the maximum value of $\bar{w}_{gc}$ is achieved when $\phi = 0.6$. Only when $E = 2$ and when $E = 4$ does obligate sex appear to be the best strategy, after accounting for the cost of sex.

DISCUSSION

In this paper we have developed a model in which fitness-altering mutations arise in a finite population. The model includes a mutation scheme that is inspired by the ideas of R. A. FISHER (1930). This mutation scheme allows for the establishment of what is apparently a stationary distribution in which mean fitness fluctuates, but does not undergo a steady increase or decrease. This is an improvement over many previous finite-population models, as they often assume that only deleterious mutations are possible, and thus, they lead

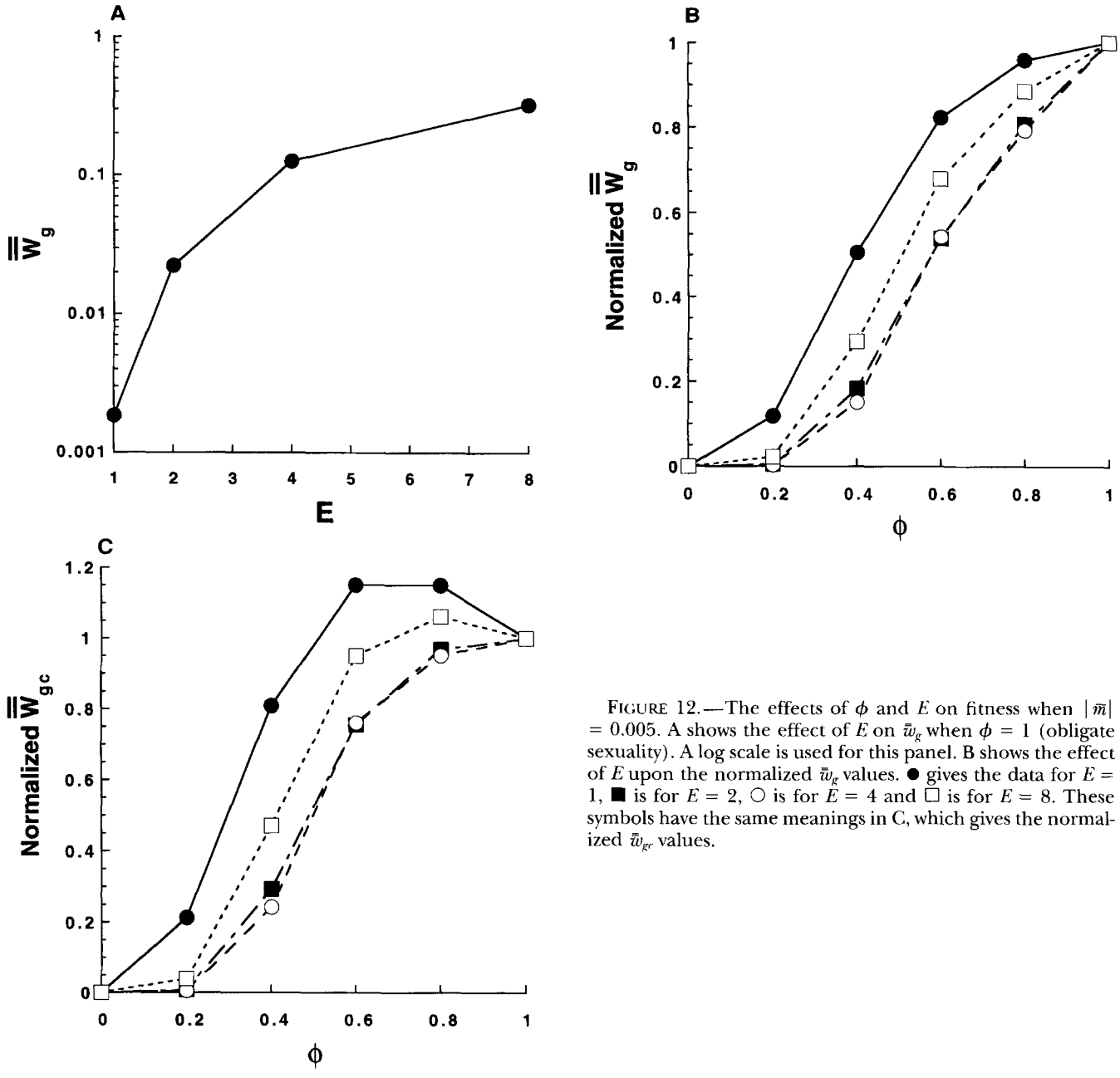

FIGURE 12.—The effects of ϕ and E on fitness when $|\bar{m}| = 0.005$. A shows the effect of E on $\bar{w}_g$ when $\phi = 1$ (obligate sexuality). A log scale is used for this panel. B shows the effect of E upon the normalized $\bar{w}_g$ values. ● gives the data for $E = 1$, ■ is for $E = 2$, ○ is for $E = 4$ and □ is for $E = 8$. These symbols have the same meanings in C, which gives the normalized $\bar{w}_{gc}$ values.

to a steady decline in fitness as mutations become fixed (see CHARLESWORTH 1993 and references therein).

Our study of the model focused on understanding the determinants of mean fitness over the long term. This sort of analysis is appropriate if one wishes to predict the outcome of ecological contests between species, where the species involved have evolved in isolation for long enough so that they approach evolutionary equilibria. In the case of our hypothetical species, mean fitness corresponds to average fertility (seed output) and, other things being equal, we can expect that the species with the highest fertility will win any ecological contest. However, it is important to recognize that "other things" may not be equal at all. It may be, for example, that the species that has the lower fertility when the two species are isolated from each other will, nevertheless, prove to be the more adept competitor when the two species are brought together. This might be the case, for example, if some members of the less-fertile species carry a disease organism to which it is resistant, but which is debilitating for its competitor. Thus, calculations of mean fitness in isolated populations, like those studied here, are useful, but they are incomplete as predictors of the outcome of real competitions. A similar caveat applies to most evolution-of-sex models.

Our results show that, regardless of the value of the other parameters, increases in the proportion of offspring produced sexually (ϕ) always tended to produce an increase in $\bar{w}_g$, which is a measure of mean fitness

that is uncorrected for the cost of sex. In general, the increases in $\bar{w}_g$ tended to be largest as ϕ increased from low values (*e.g.*, from $\phi = 0$ to $\phi = 0.2$), and smallest as ϕ increased from high values (*e.g.*, from $\phi = 0.8$ to $\phi = 1.0$).

The rise in mean fitness produced by increasing levels of sexual reproduction was apparently due largely to the fact that the magnitudes of selection coefficients tended to decrease as ϕ increased. All alleles for which $|x| \neq 0$ (and thus, for which $s > 0$) are deleterious in comparison with a perfect allele (for which $x = 0$ and $s = 0$). The programs are initialized with all perfect alleles. These have all become extinct by the time a stationary distribution is established, and typically they have been replaced largely by imperfect alleles that have drifted to a high frequency. The mutation scheme used allows nearly perfect alleles ($|x| \approx 0$) to appear from time to time after the stationary distribution has been established. The fact that these nearly perfect alleles do not take over the population suggests that alleles found at a high frequency in the population are effectively neutral when compared with perfect (or near-perfect) alleles.

The decrease in mean fitness that occurs as ϕ decreases can be attributed to the so-called Hill-Robertson effect (HILL and ROBERTSON 1966). The Hill-Robertson effect refers to the interference in the response to selection between alleles that occur at different loci. The Hill-Robertson effect operates because of linkage disequilibrium between alleles that are under selection, and that occur at different sites. In the case of the model under study here, linkage disequilibrium is generated by stochastic forces, which are due to the finite population size.

The interference described by the Hill-Robertson effect can be seen as a decrease in effective population size (N_e) (CABALLERO 1994). This decrease is accentuated when there is a high degree of correlation between the fitness of parents and the fitness of their offspring (NEI and MURATA 1966; CABALLERO 1994). This is because, if the correlation is very high, then only individuals that have a relatively high fitness have a substantial chance of having descendants in the distant future. If the correlation is weak, then even a low-fitness individual can have descendants in the distant future, because they have a nonnegligible chance of producing descendants with average or above-average fitness. Thus, a high level of correlation between parental fitness and the fitness of offspring tends to decrease effective population size.

The correlation in fitness between parents and offspring should be much larger under asexuality than under sexuality. When offspring are produced asexually, their genetically determined fitness is identical to that of their parent, except for the effects of new mutations. Thus, as ϕ declines, the range of alleles that are effectively neutral, and that can thus drift to a high frequency, is widened. [Effectively neutral alleles are generally considered to be those with selection coefficients in the range $0 < s < 1/(2N_e)$ (KIMURA 1983)].

A similar explanation can account for the observed decline in $\bar{w}_g$ with r (the rate of recombination between adjacent sites). Consider a particular site within the genome. The smaller the value of r, the more likely it is that alleles at this site will be passed to offspring along with the alleles that were adjacent to the site in the parent. Thus, the correlation between parents and offspring in the average selection coefficient for alleles near to the site is enhanced by a decline in r. To put this another way, the Hill-Robertson effect is strongest when alleles at different sites tend to stick together, and this tends to happen when r is small.

The magnitude of N_e does not depend only on the correlation in fitness between parents and their offspring. It also depends, of course, on N, the actual size of the population. As one would expect, the results show that a decrease in N produces an increase in $\bar{s}$, and thus a decrease in $\bar{w}_g$.

Theory predicts that the magnitude of N_e will depends on V_w, the coefficient of variation in fitness (NEI and MURATA 1966; CABALLERO 1994). In particular, theory suggests that N_e should fall as V_w rises. As we have seen, there are two variables that are strongly and directly related to V_w. These are U (the genomic rate of mutation) and $|m|$ (the average effect of mutations). The results show that an increase in either of these variables can produce an increase in $\bar{s}$, and a decrease in $\bar{w}_g$.

The effect of $|m|$ on average fitness may be surprising, at least at first glance. We found the lowest levels of average fitness when $|m|$ was largest (*i.e.*, when mutations had their largest effects). In contrast, studies of finite populations in which all mutations are assumed to be deleterious have generally found that mutations have their most devastating effect when they are intermediate in magnitude, and that large-effect mutations are less damaging (CHARLESWORTH *et al.* 1993; GABRIEL *et al.* 1993; LANDE 1994; LYNCH *et al.* 1995). However, this difference is more apparent than real.

In studies of finite populations where only deleterious mutations are allowed, average fitness declines forever (or until the population goes extinct). As a result, reports of these studies tend to focus on the rate of decline in fitness. Small-effect mutations have little effect on fitness, and large-effect mutations rarely go to high frequency. Thus, the fastest rate of decline in fitness (or the shortest time to population extinction) occurs for intermediate mutational effects.

On the other hand, in our study, we allowed for both beneficial and deleterious mutations, and so the population can come to a stationary distribution where mean fitness does not increase or decrease over the long term. We focused on measuring the average fitness at this stationary distribution, rather than on the rate of de-

cline. Thus, the main dependent variables reported are different in our study, as compared to studies where only deleterious mutations are allowed, and this accounts for the apparent difference in findings regarding the effects of increasing the magnitude of mutations. Furthermore, there is evidence that suggests comparable results when comparable measures are taken. Recall that, when we used the largest value of $|m|$ studied ($|m| = 0.281$) it was necessary to run an unusually large number of generations before a stationary distribution was achieved. This shows that, in our study, large-effect mutations slow the rate of decline in fitness, just as in the studies that allow only deleterious mutations. However, while large-effect mutations do slow the decline in fitness, our results show that they also lead to a relatively low level of fitness, once a stationary distribution is finally achieved.

The results presented here suggest that, when the parameters are changed in a way that increases $\bar{V}_w$, sex becomes more effective at improving mean fitness. This appears to be true, for example, when $\bar{V}_w$ increases because of increases in U or increases in $|\bar{m}|$. In addition, the results suggest that sex becomes more effective when the population size (N) decreases. Thus, it is tempting to suggest that anything that decreases N_e will make sex more effective at improving fitness. Such a relationship seems to make sense. If N_e is extremely large even when the population is asexual ($\phi = 0$), then even if a transition to obligate sexuality would produce a large increase in N_e, the increase in fitness ($\bar{w}_g$) would not be very large, because fitness would already be too close to its maximum possible value under asexuality.

A problem for the foregoing interpretation has to do with the results from the set of simulations in which the rate of recombination was manipulated. Decreasing the rate of recombination (r) might be expected to decrease N_e, and this idea is supported by the observation that a decrease in r was seen to increase the value of $\bar{s}$. Nevertheless, there is no clear and apparent trend in the effectiveness of sex as an enhancer of fitness as a function of r. Perhaps this is because a decrease in r makes sex less effective as a mechanism for reassortment of genes, and this makes it less effective as an enhancer of fitness. This effect might counteract any enhancement in the effectiveness of sex produced by the decreased value of N_e that results from a decrease in r.

Qualitatively speaking, increasing the number of sites under selection (L) has a similar effect on $\bar{w}_g$ as increasing U or $|m|$, or decreasing N. In particular, the effect is to decrease $\bar{w}_g$ when $\phi = 1$, and to increase the effectiveness of sex as an enhancer of fitness. Nevertheless, we feel that a different mechanism is at work than in the case of U, $|m|$ and N.

To understand the effects of changing the value of L, it is useful to consider, once again, KIMURA's idea about effectively neutral alleles (KIMURA 1983). KIMURA's results lead to the expectation that mutations that have drifted to a high frequency will have associated selection coefficients in the range $0 < s < 1/(2N_e)$. If fitness is largely determined by the effects of alleles that have drifted to high frequency, then KIMURA's results can be used to explain the effects of L.

To make the foregoing more clear, it helps to consider a highly contrived situation. Let us ignore alleles that have recently arisen as a result of mutation, and let us also ignore all variation among alleles that have drifted to high frequencies. Say that, when $\phi = 1$, all alleles segregating in the population have a selection coefficient given by s_1. Thus, the fitness of this population (denoted by $\bar{w}_{1.0}$) is given by $\bar{w}_{1.0} = (1 - s_1)^{2L}$. Assume further that, if ϕ is decreased to 0.8, then the resulting decline in effective population size will cause an increase in the value of the selection coefficient associated with segregating alleles to s_2 (where $s_2 > s_1$). Thus, the average fitness of this partially sexual population (denoted by $\bar{w}_{0.8}$) is given by $\bar{w}_{0.8} = (1 - s_2)^{2L}$. The ratio of $\bar{w}$ values in the sexual population and the partially asexual population is given by

$$\frac{\bar{w}_{1.0}}{\bar{w}_{0.8}} = \left[\frac{1 - s_1}{1 - s_2}\right]^{2L}. \tag{13}$$

Thus, if an increase in L has no effect at all on s_1 and s_2, it will still produce an increase in the ratio of the fitness of the sexual species over the fitness of the partially asexual species. Furthermore, this effect can be quite dramatic. If, for example, $s_1 = 0.0038$ and $s_2 = 0.0040$ (figures drawn from the results of the trials using the standard parameter values) then the ratio of $\bar{w}$ values for $L = 1000$ is 1.5, but raising L to 2000 gives a ratio of 2.2.

Of course, this explanation for the effects of L depends on N_e being small enough so that alleles that have drifted to a high frequency will have associated selection coefficients that are sufficiently large to have major effects upon fitness. If N_e is sufficiently large, then this will not be the case, and fitness will be largely determined by the effects of alleles that have recently arisen as a result of mutation, and that have a negligible chance of ever drifting to high frequency.

We believe that the process illustrated by Equation 13 constitutes the main reason for the effect of L upon the effectiveness of sex as an enhancer of fitness. However, there are clearly other things going on. For example, increasing L decreases the between-site rate of recombination, as more loci are packed onto each chromosome. Perhaps more importantly, an increase in L decreases the allelic mutation rate, because the number of loci increases while the genomic mutation rate stays the same. It seems likely that this explains the small increase in $\bar{s}$ that occurs as L is decreased from $L = 2000$ to $L = 1000$, and the larger increase that occurs

as L is decreased from $L = 1000$ to $L = 240$ (see Table 1). The increase in the allelic mutation rate that is associated with a decrease in L can be expected to lead to more segregating alleles that have recently arisen from mutation, and thus to fewer segregating alleles that have drifted to high frequency over a relatively long period of time. These recently arisen alleles can be expected to be associated with larger selection coefficients (on average) than alleles that have drifted to high frequency, despite the rigours of selection. Support for this explanation for the relationship between L and $\bar{s}$ comes from the observation that the average number of segregating alleles per locus increases as L decreases (see Table 1). This is just what one would expect if, when L is relatively small, more recently arisen alleles are segregating.

If the decrease in $\bar{s}$ with increases in L was fast enough, then sex might be more effective at enhancing fitness when L is small. However, the decrease in $\bar{s}$ with increases in L is apparently not fast enough for this to happen, and indeed, the rate of decrease in $\bar{s}$ seems to fall off as L becomes large. This suggests that increasing L to biologically realistic levels would greatly increase the effectiveness of sex as a fitness enhancer. However, no decisive comment can be made on this issue until further studies are carried out.

One characteristic of the results that makes their applicability to real-world populations somewhat doubtful is the high level of genetic load observed in most of the simulations. A quick examination of Table 1 reveals that load is close to 1.0 (its maximum value) for all of the simulation results presented here for which there was no synergistic epistasis. Some authors claim that high load is not necessarily a substantial problem so long as the within-population variance in fitness observed is not too large (see GILLESPIE 1991 and references therein). However, the more conventional view is that models that produce a high level of load are unrealistic (KIMURA 1983).

A traditional way to deal with excessive load is to introduce synergistic epistasis (KIMURA and MARUYAMA 1966). We showed that synergistic epistasis does decrease load in the context of our model, and that this reduction can be quite dramatic. However, synergistic epistasis also introduces a variety of complex phenomena to the dynamics of the model, and we have not attempted a complete analysis here.

Our results do not show any simple relationship between the degree of synergistic epistasis and the effectiveness of sex as an enhancer of fitness. It seems likely that this is because synergistic epistasis has multiple impacts on the effectiveness of sex, and these do not all act in the same direction. For example, the results show that increasing the level of synergistic epistasis tends to increase $\bar{V}_w$, and, as noted above, this can be expected to increase the effectiveness of sex as an enhancer of fitness. Synergistic epistasis should also increase the effectiveness of sex because of the deterministic processes described by KONDRASHOV and others (KIMURA and MARUYAMA 1966; KONDRASHOV 1988; CHARLESWORTH 1990). However, because synergistic epistasis reduces load, it may also introduce a "ceiling effect." In particular, under synergistic epistasis, a given reduction in the level of genetic deterioration (D_k) has a smaller proportional effect on fitness for a relatively fit individual, as compared to an unfit individual (see Equation 12). Thus, it is not surprising to note that, under synergistic epistasis, the improvement in fitness caused by increasing the rate of sexual reproduction can be less than what is observed in a strictly multiplicative model.

With $|m|$ set to its standard value of 0.0206, we found that, for all values of E (the epistasis parameter) studied, obligate sexual reproduction produces the fittest populations, even after taking the cost of sex into account. This was so even though, as E increased, genetic load became relatively low, at least in the obligately sexual populations. However, with $|m| = 0.0206$, the coefficient of variation in fitness ($\bar{V}_w$) can be very large, and probably unrealistically so, at least for $E \gg 1$. We also studied the case where $|m| = 0.005$. This leads to much more reasonable values of $\bar{V}_w$, and genetic loads were still much reduced in comparison to a strictly multiplicative model. However, after taking the cost-of-sex into account, obligately sexual populations were the most fit only for $E = 2$ and $E = 4$. For the other values of E tested ($E = 1$ and $E = 8$) the fittest populations still had high levels of sexual reproduction, but they also engaged in some asexual reproduction.

As a result of computational limitations, the simulation studies were confined to a biologically unrealistic range of parameters. In the real world, genome sizes (L values) are generally much larger than the 1000 sites used in most of the studies presented herein. Furthermore, population sizes (N values) are typically larger, and allelic mutation rates are lower than assumed here. While faster computers would certainly help to ameliorate this problem, it seems likely that the only way to approach a realistic region of parameter space in the forseeable future is by the application of purely analytic methods, or by analysis in combination with computer-oriented methods.

Because of the unrealistic parameter values, it is difficult to know whether the results of our simulation studies can explain the success of obligate sexual reproduction in natural environments. For example, our results on the consequences of manipulating N suggest that, with the other parameters set to their standard values, an obligately sexual species is unlikely to prevail in ecological competitions when populations have more than 400 individuals apiece. However, we have also seen that increasing L (the number of sites) above the unrealistically low value of 1000 can cause a large increase in the efficacy of sex as a fitness enhancer. Thus, it may

well be that if both N and L are increased to biologically realistic levels, obligate sexuality would be favored in many cases (although this speculation is entirely unproved). Note that, if the value of U is biologically reasonable, then increasing L to a biologically realistic level would automatically decrease the allelic mutation rate to a realistic value.

It seems likely that, if we were able to increase population size (N) to an extremely large value without doing the same to L, then $\bar{w}$ would come to approximate e^{-U} (KIMURA and MARUYAMA 1966; CROW 1970). However, this relation depends on multiplicative fitness relations, and we do not expect it to hold in the case of the synergistic epistasis model.

Despite the preliminary nature of the results, it may be worthwhile to consider whether they might help us to understand the distribution of sexuality in natural environments. The results suggest that asexuality should be more common in large populations. The largest populations on earth consist of microorganisms such as bacteria, viruses, and yeast. In general, there is very little sexual reproduction within these populations [though this may be due to a low rate of mutation in these organisms (DRAKE 1991a,b; KIBOTA and LYNCH 1996)]. On the other hand, organisms that usually live in fairly small populations (*e.g.*, mammals, birds and trees) typically produce most or all of their offspring sexually. Of course, there are some exceptions to these trends, notably among the animals, where, for example, there are some insects, some lizards and some fish that apparently reproduce by entirely asexual means (SUOMALAINEN 1950). Asexuality has also arisen many times among the plants, although there seems to be a tendency for this to occur in plants that have a large range, and thus, plausibly, a large population size (BIERZYCHUDEK 1985; STEBBINS 1985). Interestingly, it appears that macroscopic asexual species tend to go extinct relatively quickly (MAYNARD SMITH 1978; BELL 1982). Thus, perhaps the population sizes of nearly all macroscopic organisms are too small to support complete asexuality over the long term. The results also suggest that asexuality should be more common among organisms with small genome sizes. Unfortunately, the smallest genomes occur in microbes, and thus there is some confounding between the predictions based on population size, predictions based on mutation rate, and predictions based on the number of loci. Both population-size considerations and genome-size considerations suggest that asexuality should be most common among microbes.

Although there appears to be a prima-facie case in favor of the theory on the basis of existing data, a great deal more work needs to be done. Fortunately, because the theory allows for consideration of the case of intermediate sexuality ($0 < \phi < 1$), it is possible to imagine tests that could be carried out within a species, and thus avoid some of the problems of confounding mentioned above. For example, it would be interesting to compare systematically long-established plant populations that are relatively small with large and long-established populations of the same species. If the theory is correct, then the large populations should be more prone to vegetative (*i.e.*, asexual) reproduction. It would also be interesting to test the theory in the microbial laboratory, perhaps using a yeast species that is competent to reproduce either sexually or asexually. One could then manipulate parameters such as population size and mutation rate to see if the rate of sexual reproduction responds in accord with predictions based on the theory.

The modeling efforts presented here are mostly relevant for predicting the outcome of competitions between species. However, it would be worthwhile to consider whether the evolutionary processes we have described might also account for the evolution and maintenance of obligate sexuality within some species. In particular, it would be interesting to study a so-called "modifier model" in which a gene that alters the probability of producing offspring sexually is introduced into a population. Despite the strong effects of altering ϕ observed in the simulation studies, it is entirely possible that investigation of modifier models would lead to the conclusion that individual selection in a homogeneous environment cannot lead to the evolution and maintenance of obligate sexual reproduction. If this is the outcome, then it might be useful to consider heterogeneous environments, since these could slow the spread of asexuality and enhance correlations within the metapopulation between modifier alleles and selected alleles. It might also be worthwhile to study a multiple-species model that allows for variation in the tendency to produce sexually both within species and between species. It appears that such models may allow for the evolution and persistence of obligate sexuality, even when this is not possible with a single-species model (NUNNEY 1989; WILLIAMS 1992).

Our study is related to various pieces of previously published work on the evolution of sex. For example, a similar process to the one we have described is in operation in Muller's Ratchet models. Like our own model, Muller's Ratchet models operate in finite populations, and they incorporate FAMs. However, unlike our model, Muller's Ratchet models typically assume that all FAMs are deleterious, and that they are all equal in effect (MULLER 1964; HAIGH 1978; CHARLESWORTH *et al.* 1993). The results from these models suggest that, under asexuality, deleterious mutations with a substantial effect can become effectively neutral, and thus can rise to a high frequency. Unfortunately, because only deleterious mutations are allowed in the traditional Muller's Ratchet models, these models lead to the genetic degeneration of sexual populations as well as asexual populations, although much larger amounts of time are typically required for degeneration under obligate sexuality (CHARLESWORTH *et al.* 1993). Another prob-

lem with traditional Muller's Ratchet models as explanations for obligate sexuality is that it appears that a small amount of recombination (and thus, by implication, sexuality) is all that is required to slow the rate of genetic degradation to a level that is close to what is achieved under free recombination and obligate sex (CHARLESWORTH *et al.* 1993). It seems likely that this is due to the fact that traditional Muller's Ratchet models do not allow for the occurrence of a continuous range of effects of FAMs, with some of them having only a very small effect on fitness [although a paper by BUTCHER (1995) is an exception].

Of all the work on the evolution of sex, the model that seems to be closest to our own was studied by WAGNER and GABRIEL (1990). They examined an asexual species with stabilizing selection acting independently on C different characters. Their model was not explicitly genetic, and they assumed that mutations affect all characters at once. Mutations to each character were normally distributed around the current value of the character.

Like the model studied here, WAGNER and GABRIEL's model allows for the occurrence of very-small-effect mutations. Thus, one might expect that their results would be similar to our own, at least for the case of asexuality. However, at first reading, this does not appear to be the case. In their abstract, WAGNER and GABRIEL seem to imply that for some choices of parameters, the optimal phenotype can persist forever. However, a close reading of their paper suggests that they know this cannot be the case, as they cite previously published work that calculates the number of generations required for extinction of the optimal genotype. They publish two figures that appear to show stable persistence of the optimal phenotype, but in these two cases the average mutation to an optimal individual produces decreases in fitness of $\approx$18% and $\approx$32%, respectively. Furthermore, the normal distribution used for mutant effects, along with the fact that all characters mutate at once, means that very-small-effect mutants, while possible, are very rare. WAGNER and GABRIEL only carry out 300 generations of evolution in the simulations that show persistence of the optimal phenotype, and this, along with the other factors just mentioned, probably accounts for their results. We feel certain that, if they had run their simulations for a much longer period, they would have observed extinction of the optimal phenotype in all cases.

WAGNER and GABRIEL also report one case where the optimal phenotype went extinct. In agreement with our results, they show that the fitness of the population appears to reach a stationary distribution in this case. However, they claim that, once the stationary distribution is reached, the average "distance" of individuals' phenotypes from the optimum is the similar to the case of a sexual population. Unfortunately, the only support they produce for this claim is a comparison with a paper by LANDE (1976). The model studied by LANDE is very different from the one studied by WAGNER and GABRIEL. For example, LANDE does not explicitly incorporate mutation into his model. Furthermore, WAGNER and GABRIEL do not make it clear how they made their comparison. For these reasons we feel that WAGNER and GABRIEL's claim that their model produces similar results for sexuals and asexuals must be viewed with extreme circumspection, at least until a sexual version of their model has been constructed.

In this paper we have seen that, in some circumstances, sexual reproduction can produce very large enhancements in fitness. It appears that this occurs because sex increases effective population size (N_e). With this in mind, it is worth considering the very wide range of traits other than sexual reproduction that can also alter effective population size (CROW and KIMURA 1970; CABALLERO 1994). Any trait that enhances variance in reproductive success will decrease N_e. Such traits include mating preferences and competition among same-sex individuals for mates. The value of N_e is also under the control of behavioral preferences for life in small or large subpopulations, migratory behavior, tendencies to produce biased sex ratios among offspring, and many other traits. The effects of drift load have not been widely considered in discussions of N_e affecting traits. However, the results we have presented suggest that even traits that have a small effect on N_e may have large effects on fitness. Thus, consideration of the impact of drift load on the outcome of evolution may help us to understand the evolution of a wide variety of different phenotypic characters.

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LITERATURE CITED

ANTEQUERA, F., and A. BIRD, 1993 Number of CpG islands and genes in human and mouse. Proc. Natl. Acad. Sci. USA **90:** 11995–11999.

ASSOUAD, M. W., B. DOMMÉE, R. LUMARET and G. VALDEYRON, 1978 Reproductive capacities in the sexual forms of the gynodioecious species *Thymus vulgaris L.* Bot. J. Linn. Soc. **77:** 29–39.

BARTON, N. H., 1986 The maintenance of polygenic variation through a balance between mutation and stabilizing selection. Genet. Res. **47:** 209–216.

BELL, G., 1982 *The Masterpiece of Nature.* University of California Press, San Francisco.

BELL, G., 1988 Recombination and the immortality of the germ line. J. Evol. Biol. **1:** 67–82.

BERNSTEIN, H., F. A. HOPF and R. E. MICHOD, 1988 Is meiotic recombination an adaptation for repairing DNA, producing genetic variation, or both?, pp. 139–160 in *The Evolution of Sex: An Examination of Current Ideas,* edited by R. E. MICHOD and B. R. LEVIN. Sinauer, Sunderland, MA.

BIERZYCHUDEK, P., 1985 Patterns in plant parthenogenesis. Experientia **41:** 1255–1263.

BULMER, M. G., 1989 Maintenance of genetic variability by mutation-selection balance: a child's guide through the jungle. Genome **31:** 761–767.

BÜRGER, R., G. P. WAGNER and F. STETTINGER, 1989 How much heritable variation can be maintained in finite populations by mutation-selection balance? Evolution **43:** 1748–1766.

BUTCHER, D., 1995 Muller's ratchet, epistasis and mutation effects. Genetics **141:** 431–437.

CABALLERO, A., 1994 Developments in the prediction of effective population size. Heredity **73:** 657–679.

CHARLESWORTH, B., 1987 The heritability of fitness, pp. 21–40 in *Sexual Selection: Testing the Alternatives,* edited by J. W. Bradbury and M. B. Andersson. John Wiley & Sons, New York.

CHARLESWORTH, B., 1990 Mutation-selection balance and the evolutionary advantage of sex and recombination. Genet. Res. **55:** 199–221.

CHARLESWORTH, B., and D. CHARLESWORTH, 1981 Allocation of resources to male and female functions in hermaphrodites. Biol. J. Linn. Soc. **15:** 57–74.

CHARLESWORTH, B., D. CHARLESWORTH and M. T. MORGAN, 1990 Genetic loads and estimates of mutation rates in highly inbred plant populations. Nature **347:** 380–382.

CHARLESWORTH, D., M. T. MORGAN and B. CHARLESWORTH, 1993 Mutation accumulation in finite outbreeding and inbreeding populations. Genet. Res. **61:** 39–56.

CHARNOV, E. L., 1982 *The Theory of Sex Allocation.* Princeton University Press, Princeton.

CROW, J. F., 1970 Genetic loads and the cost of natural selection, pp. 128–177 in *Mathematical Topics in Population Genetics,* edited by K. KOJIMA. Springer-Verlag, Berlin.

CROW, J. F., 1979 Minor viability mutants in *Drosophila.* Genetics **92:** s165-s172.

CROW, J. F., and M. KIMURA, 1970 *An Introduction to Population Genetics Theory.* Burgess, Minneapolis.

CROW, J. F., and M. J. SIMMONS, 1983 The mutation load in *Drosophila,* pp. 2–35 in *The Genetics and Biology of Drosophila,* Vol. 3c, edited by M. ASHBURNER, H. L. CARSON and J. N. THOMPSON. Academic Press, New York.

DAVISSON, M. T., and T. H. RODERICK, 1990 Linkage map, pp. 416–427 in *Genetic Variants and Strains of the Laboratory Mouse,* Ed. 2, edited by M. F. LYON and A. G. SEARLE. Oxford University Press, Oxford.

DE VISSER, J. A. G. M., R. F. HOEKSTRA and H. VAN DEN ENDE, 1996 The effect of sex and deleterious mutations on fitness in *Chlamydomonas.* Proc. R. Soc. Lond. B **263:** 193–200.

DRAKE, J. W., 1991a A constant rate of spontaneous mutation in DNA-based microbes. Proc. Natl. Acad. Sci. USA **88:** 7160–7164.

DRAKE, J. W., 1991b Spontaneous mutation. Annu. Rev. Genet. **25:** 125–146.

FELSENSTEIN, J., 1974 The evolutionary advantage of recombination. Genetics **78:** 737–756.

FELSENSTEIN, J., and S. YOKOYAMA, 1976 The evolutionary advantage of recombination II. Individual selection for recombination. Genetics **83:** 845–859.

FISHER, R. A., 1930 *The Genetical Theory of Natural Selection.* Clarendon Press, Oxford.

GABRIEL, W., M. LYNCH and R. BÜRGER, 1993 Muller's Ratchet and mutational meltdowns. Evolution **47:** 1744–1757.

GILLESPIE, J. H., 1991 *The Causes of Molecular Evolution.* Oxford University Press, Oxford.

GREEN, R. F., and D. L. G. NOAKES, 1995 Is a little bit of sex as good as a lot? J. Theoret. Biol. **174:** 87–96.

HAIGH, J., 1978 The accumulation of deleterious genes in a population—Muller's ratchet. Theoret. Popul. Biol. **14:** 251–267.

HAMILTON, W. D., R. AXELROD and R. TANESE, 1990 Sexual reproduction as an adaptation to resist parasites (a review). Proc. Natl. Acad. Sci. USA **87:** 3566–3573.

HILL, W. G., and J. RABASH, 1986 Models of long term artificial selection in finite population. Genet. Res. **48:** 41–50.

HILL, W. G., and A. ROBERTSON, 1966 The effect of linkage on limits to artificial selection. Genet. Res. **8:** 269–294.

HOULE, D., D. K. HOFFMASTER, S. ASSIMACOPOULOS and B. CHARLESWORTH, 1992 The genomic mutation rate for fitness in *Drosophila.* Nature **359:** 58–60.

HURST, L. H., and J. R. PECK, 1996 Recent advances in understanding of the evolution and maintenance of sex. Trends Ecol. Evol. **11:** A46-A52.

KEIGHTLEY, P. D., 1994 The distribution of mutation effects on viability in *Drosophila melanogaster.* Genetics **138:** 1315–1322.

KEIGHTLEY, P. D., and W. G. HILL, 1987 Directional selection and variation in finite populations. Genetics **117:** 573–582.

KEIGHTLEY, P. D., and W. G. HILL, 1988 Quantitative genetic variability maintained by mutation-stabilizing selection balance in finite populations. Genet. Res. **52:** 33–43.

KIBOTA, T. T., and M. LYNCH, 1996 The deleterious genomic mutation rate for overall fitness in *Escherichia coli.* Nature **381:** 694–696.

KIMURA, M., 1983 *The Neutral Theory of Molecular Evolution.* Cambridge University Press, Cambridge.

KIMURA, M., and T. MARUYAMA, 1966 The mutational load with epistatic gene interactions in fitness. Genetics **54:** 1337–1351.

KIMURA, M., and T. OHTA, 1970 Genetic loads at a polymorphic locus which is maintained by frequency-dependent selection. Genet. Res. **16:** 145–150.

KINGMAN, J. F. C., 1978 A simple model for the balance between selection and mutation. J. Appl. Prob. **15:** 1–12.

KONDRASHOV, A. S., 1984 Deleterious mutations as an evolutionary factor. I. The advantage of recombination. Genet. Res. Camb. **44:** 199–217.

KONDRASHOV, A. S., 1988 Deleterious mutations and the evolution of sexual reproduction. Nature **336:** 435–440.

KONDRASHOV, A. S., 1994 Muller's ratchet under epistatic selection. Genetics **136:** 1469–1473.

KONDRASHOV, A. S., 1995 Contamination of the genome by very slightly deleterious mutations—why have we not died 100 times over? J. Theoret. Biol. **175:** 583–594.

KONDRASHOV, A. S., and M. TURELLI, 1992 Deleterious mutations, apparent stabilizing selection and the maintenance of quantitative variation. Genetics **132:** 603–618.

LANDE, R., 1976 Natural selection and random genetic drift in phenotypic evolution. Evolution **30:** 314–334.

LANDE, R., 1994 Risk of population extinction from fixation of new deleterious mutations. Evolution **48:** 1460–1469.

LLOYD, D. G., 1976 The transmission of genes via pollen and ovules in gynodioecious angiosperms. Theoret. Popul. Biol. **9:** 229–316.

LYNCH, M., and W. GABRIEL, 1990 Mutation load and the survival of small populations. Evolution **44:** 1725–1737.

LYNCH, M., J. CONERY and R. BÜRGER, 1995 Mutational meltdowns in sexual populations. Evolution **49:** 1067–1080.

MACKAY, T. F. C., R. F. LYMAN and M. S. JACKSON, 1992 Effects of *P* element insertions on quantitative traits in *Drosophila melanogaster.* Genetics **130:** 315–332.

MAYNARD SMITH, J., 1978 *The Evolution of Sex.* Cambridge University Press, Cambridge.

MAYNARD SMITH, J., and J. HAIGH, 1973 The hitch-hiking effect of a favourable gene. Genet. Res. **23:** 23–35.

MICHOD, R. E., and T. W. GAYLEY, 1992 Masking of mutations and the evolution of sex. Am. Nat. **139:** 706–734.

MICHOD, R. E., and B. R. LEVIN, 1988 *The Evolution of Sex: An Examination of Current Ideas.* Sinauer, Sunderland, MA.

MUKAI, T., 1964 The genetic structure of natural populations of *Drosophila melanogaster.* I. Spontaneous mutation rate of polygenes controlling viability. Genetics **50:** 1–19.

MUKAI, T. S., S. J. CHIGUSA, L. E. METTLER and J. F. CROW, 1972 Mutation rate and dominance of genes affecting viability in *Drosophila melanogaster.* Genetics **72:** 339–355.

MULLER, H. J., 1932 Some genetic aspects of sex. Am. Nat. **66:** 118–138.

MULLER, H. J., 1964 The relation of recombination to mutational advance. Mutat. Res. **1:** 2–9.

NEI, M., and M. MURATA, 1966 Effective population size when fertility is inherited. Genet. Res. **8:** 257–260.

NOWAK, R., 1994 Mining treasures from 'junk DNA'. Science **263:** 608–610.

NUNNEY, L., 1989 The maintenance of sex by group selection. Evolution **43:** 245–257.

OHTA, T., 1992 The nearly neutral theory of molecular evolution. Annu. Rev. Ecol. Systematics **23:** 263–286.

OHTA, T., and H. TACHIDA, 1990 Theoretical study of near neutrality. I. Heterozygosity and rate of mutant substitution. Genetics **126:** 219–229.

PAMILO, P., M. NEI and W. H. LI, 1987 Accumulation of mutations in sexual and asexual populations. Genet. Res. **49:** 135–146.

PECK, J. R., 1994 A ruby in the rubbish: beneficial mutations, deleterious mutations and the evolution of sex. Genetics **137:** 597–606.

ROSE, M. R., 1983 The contagion mechanism for the origin of sex. J. Theoret. Biol. **101:** 137–146.

SHIELDS, R., 1993 Pastoral synteny. Nature **365:** 297–298.

SIMMONS, M. J., and J. F. CROW, 1977 Mutations affecting fitness in *Drosophila* populations. Annu. Rev. Genet. **11:** 49–78.

STEBBINS, G. L., 1985 *Chromosomal Evolution in Higher Plants.* Addison Wesley, Reading, MA.

SUOMALAINEN, E., 1950 Parthenogenesis in animals. Adv. Genet. **3:** 193–253.

SZATHMÁRY, E., 1993 Do deleterious mutations act synergistically? Metabolic control theory provides a partial answer. Genetics **133:** 127–132.

TACHIDA, H., 1991 A study on a nearly neutral mutation model in finite populations. Genetics **128:** 183–192.

TAUTZ, D., 1992 Redundancies, development and the flow of information. BioEssays **14:** 263–266.

THOMAS, J. H., 1993 Thinking about genetic redundancy. Trends Genet. **9:** 395–399.

TURELLI, M., 1984 Heritable genetic variation via mutation-selection balance: Lerch's zeta meets the abdominal bristle. Theoret. Popul. Biol. **25:** 138–193.

VAN DAMME, J. M. M., and W. VAN DELDEN, 1984 Gynodioecy in *Plantago Lanceolata* L. IV. Fitness components of sex types in different life cycle stages. Evolution **36:** 1326–1336.

WAGNER, G. P., and W. GABRIEL, 1990 Quantitative variation in finite parthenogenetic populations: what stops Muller's ratchet in the absence of recombination? Evolution **44:** 715–731.

WEISMANN, A., 1889 *Essays Upon Heredity and Kindred Biological Problems.* Clarendon Press, Oxford.

WILLIAMS, G. C., 1992 *Natural Selection: Domains, Levels, and Challenges.* Oxford University Press, Oxford.

ZENG, Z. B., and C. C. COCKERHAM, 1993 Mutation models and quantitative genetic variation. Genetics **133:** 729–736.

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