DOES SEX ACCELERATE EVOLUTION?

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ABSTRACT: Most biologists believe that sex (recombination) accelerates adaptation and evolution by speeding response to directional selection. This belief does not hold up under close scrunity. Several experiments, a number of computer simulations, and various works of theory all suggest that sex will accelerate response to selection only when populations are very small or when they exhibit substantial negative linkage disequilibrium. Neither condition appears to be especially common in nature, so the role of sex in evolution remains enigmatic. Models invoking migration and mixing of populations or temporally fluctuating environments may offer a way out, but the assumptions on which they are based are largely untested. Sex may act most often to slow or moderate response to selection, directly contradicting the notions that now prevail. Several unsettled points must be resolved before we can adequately assess the role of sex in nature, among them: (1) Does evolution proceed primarily through the reassortment of genes pre-existing at high frequency or does it proceed through the combination and spread of new or previously rare mutations? (2) Are complex inter-locus interactions or additive gene effects the rule in nature? (3) Are asexual populations regularly genetically impoverished? (4) Does group selection play an important role in evolution?

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Sex, genetic recombination, is a randomizing process, reshuffling genes among genomes and tearing apart orderly associations of alleles at different loci. But biologists regularly assign to sex an apparently opposite role, a constructive role, in nature. They hold up sex as the primary source of novel genotypes and the single major mechanism facilitating progressive evolution. The first assertion must be true for most macroscopic organisms, the second is probably false. Because, contrary to prevailing belief, there is little or no evidence that sex speeds genetic adaptation to changed or changing environments. In this paper I summarize the history of evolutionary interpretations of sex and present some evidence that sex may most often facilitate evolution by slowing it down.

The Historical Setting

Most populations of organisms participate in sexual processes, some each generation, some intermittently. But historically biologists were slow to recognize the ubiquity of sex (Olby, 1966). They did not recognize plants as sexual beings until the end of the seventeenth century, and they overlooked the sexual nature of protozoan conjugation until the end of the nineteenth century. Recombination processes in bacteria and viruses have been elucidated only in the last three decades. Nevertheless, omitting the special case of microorganisms, the near universality of sexual processes became a well entrenched tenent of biology by the mid-nineteenth century. The burden of proof fell on those who doubted its applicability to particular cases. Paradoxically, recognition of the ubiquity of sex suppressed serious inquiry into its fundamental nature. Sex appeared to be co-extensive with life and many

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biologists interpreted fertilization as a semi-mystical life-renewing phenomenon. Even in the late nineteenth century, as the cytological facts of fertilization were unveiled, this attitude lingered on in the rejuvenescence theories of Maupas, Bütschli, and Hertwig (Jennings, 1929; Weismann, 1892).

But mid-nineteenth century discoveries of several cases of parthenogenesis and apomixis in higher organisms left open the possibility of interest in biparental reproduction as a thing in itself. If sex could be dispensed with after all, the reasons underlying its persistence in most organisms became a valid subject of inquiry. After Darwin biologists could seek evolutionary bases for the retention of sex. The task fell initially to August Weismann, a German cytologist.

Early in his evolutionary studies Weismann concluded that external factors must have no influence on the hereditary disposition of organisms, that acquired characteristics are not inherited. He championed this idea so forcefully that his name became synonymous with anti-Lamarckism in the popular lore of science. Weismann's strong anti-Lamarckian stand raised anew a major question that Darwin never adequately resolved, the source of hereditary variation. "How," Weismann asked, "can deep-seated hereditary characters arise at all, if they are not produced by the external influences to which the individual is exposed?" The source of hereditary variation, he answered:

> "is to be looked for in the form of reproduction by which the great majority of existing organisms are propogated: viz., in sexual reproduction, or, as Häckel calls it amphigonic reproduction. . . in amphigonic reproduction two groups of hereditary tendencies are as it were combined. I regard this combination as the cause of hereditary individual characters, and I believe that the production of such characters is the true significance of amphigonic reproduction. The object of this process is to create those individual differences which form the material out of which natural selection produces new species" (Weismann, 1891, p. 279).

In other words Weismann postulated that sexual reproduction generates the genetic variation that forms the raw material of natural selection.

The observation that sexual reproduction generates hereditary diversity was not original to Weismann. Plant breeders had been aware of this fact for quite a long time and the physician Erasmus Darwin (grandfather of Charles) had set it down in the scientific literature in the late eighteenth century, complete with a theory that asexual propagation is coupled with an inability to evolve novel or improved forms (Darwin, 1796, pp. 491, 523). Charles Darwin himself at first adhered to his grandfather's views on sex (De Beer, 1960a, p. 41), but later in life he repudiated the idea that crossing is the major source of hereditary variation (Darwin, 1876, Vol. I pp. 197, 398, Vol. II pp. 242, 252) and adopted a very different view of the role of sex in nature. Weismann's contribution lay in uniting the facts of sexual reproduction with a coherent theory of heredity and anchoring both in evolutionary theory. Our contemporary understanding of the evolutionary role of sex begins with Weismann and his works on the subject still deserve study.

Given Weismann's early lead, we might suppose that the evolutionary theory of sexual reproduction would by now be fairly advanced. This is not the case. To the question posed by Weismann (and expressed succinctly by Maynard Smith, 1971b, as "what use is sex") we have yet to elaborate a really satisfactory answer. The reasons for this failure are not hard to find. In the first place sex is not an ordinary evolutionary attribute. By all appearances it confers on individual carriers an evolutionary disadvantage, sometimes a very severe one (Maynard Smith, 1971a, 1971b, 1974). Consequently many have sought,

consciously and otherwise, to find the evolutionary advantage of sex in benefits accruing to whole populations. Fisher (1958, p. 50) even suggested that sex may be the only example of a trait that has evolved for the advantage of species rather than individuals. Other commentators insist that the persistence of sex be interpreted in terms of short term individual advantage (Williams, 1966, 1975; Williams and Mitton, 1973; Ghiselin, 1974). Virtually all investigators from Weismann on (1891, pp. 288-289; 1904, p. 223) agree that sexual reproduction must have once conferred individual selective advantage, sometime in the evolutionary past. Whatever the outcome of this debate, inter-demic or "group" selection must be seriously investigated as an agent in the evolution of sex, and the ecological and evolutionary models for group selection are less well established than the traditional models for individual selection.

The second reason for our failure to establish a satisfactory explanation for sex is perhaps more fundamental. Weismann's theory and its subsequent Mendelian elaborations (for an early example see East, 1918) predict that sexual admixture of genomes will generate hereditary variability and promote the formation of novel hereditary combinations. But every theory of sexual advantage must hypothesize the nature of the genetic variation on which sexual systems operate. Weismann simply assumed that because natural selection has worked such tremendous change in the organic world, the store of standing genetic variation must be very large and must be available to sexual crossing and selection. However, the precise nature of the genetic variation on which sex operates should, as we shall see, profoundly affect the role of sex in evolution. And regarding the nature of selectable variation, population biologists do not agree. They divide into two camps. The substance of the disagreement between these schools appears in especially sharp relief in their contrasting attitudes towards the evolutionary advantage of sex (Crow and Kimura, 1970, pp. 313-316; Lewontin, 1974, p. 196). They appeal to very different models of standing genetic variation in natural populations. Consequently, they construct very different models regarding the benefits of biparental reproduction.

The Fisher-Muller Mutation Theory of Sexual Advantage

The most coherent contemporary theory of sexual advantage derives from early work by Fisher (1930) and Muller (1932). They argued that in asexual populations two or more different advantageous mutations can be incorporated only if they occur simultaneously in the same individual or sequentially in the same clone. Since mutation rates are low, sequential incorporation must be the rule, and the incorporation of several mutations must be a slow and inefficient process. In sexual populations favorable mutations occurring during a given time period in different individuals may be brought together in their descendants. All other things being equal, sexual populations should incorporate combinations of favorable mutations more rapidly than their asexual counterparts.

Several authors have developed and quantified the Fisher-Muller argument (Muller, 1958, 1964; Crow and Kimura, 1965, 1969; Bodmer, 1970; Maynard Smith, 1971b, 1974; Karlin, 1973; Felsenstein, 1974; Nyberg, 1975). Ulam (1967), Schrandt and Ulam (1971), and Reed, Toombs and Barricelli (1967) have also developed ideas along similar lines. Although in premises and detailed results these works differ in significant respects, they share: 1) the assumption that initial gene frequencies of favored alleles are very small, and 2) the conclusion that sexual reproduction can substantially accelerate the rate of evolution. In all these models evolution depends on the spread of rare favorable mutations of small effect. They accept implicitly the classical theory of population structure (Dobzhansky, 1955, 1970; Lewontin, 1974), which postulates that the preponderance of selectively relevant genetic variation in a local population consists at any given time of a few favored alleles on their way towards fixation.

Even granted the questionable premises of the classical theory, the Fisher-Muller argument may be more restricted in application than its proponents have generally recognized. Using a deterministic haploid two-locus model, Eshel and Feldman (1970) have demonstrated that the postulated advantage of sexual reproduction may depend on rather special fitness relationships between loci. They consider a population initially consisting entirely of AB genotypes. A mutates at a low rate to a and B to b, with fitness relationships as follows:

Genotype	AB	Ab	aB	ab
Fitness	1	s_2	s_2	s_1

Eshel and Feldman show that if the mutations are individually deleterious but advantageous in combination ($s_2 < 1 < s_1$), and provided that the loci freely recombine and mutation rates are sufficiently small, the double mutant can never increase in frequency much beyond the order of the mutation rate. In an asexual (non-recombining) population, by contrast, the double mutant, when it occurs, will increase to fixation. Karlin and McGregor (1971) have extended this result to two-locus diploid systems. Muller himself recognized this theoretical pitfall. It drove him to argue that the prevalence of sexual reproduction testifies in itself to the leading role of "additive" genetic effects in evolution (Muller, 1958, 1964).

But Eshel and Feldman analyze another set of relations that cast even greater doubt on the generality of the Fisher-Muller theory. Suppose that both mutations are beneficial and that in combination they are more beneficial than either alone ($s_2 > 1$, $s_1 > 1$, $s_1 > s_2$). Maynard Smith (1968) has shown that in this case when fitnesses are multiplicative ($s_2^2 = s_1$) sexual and asexual populations will incorporate the double mutant at exactly the same rate. This, Eshel and Feldman point out, is a very special case. If fitnesses are "super-multiplicative" ($s_2^2 < s_1$) the frequency of double mutants will actually increase more rapidly in asexual populations. Only in the case that fitnesses are "submultiplicative" ($s_2^2 > s_1$) will sexual populations incorporate the double mutant more rapidly.

The submultiplicative case includes one very important subcase, the case of strict additivity of effects. Let $s_2 = 1 + x$. For multiplicative fitnesses $s_1 = 1 + 2x + x^2$. For additive fitnesses $s_1 = 1 + 2x$. Additive fitnesses are always submultiplicative. Note that as the advantages associated with single mutations become very small, multiplicative fitnesses converge towards the additive case. Not only are the advantages of recombination restricted to a narrow range of fitness relationships between loci, they tend to disappear the more closely the loci under selection approach one assumption of the classical hypothesis, relatively small fitness differences between alleles.

Using haploid two-locus models Karlin (1973) has extended Eshel and Feldman's work to finite populations. Recombination, he finds, tends to speed the first appearance of double mutants in populations, but tends to slow down their subsequent rate of incorporation, even in the absence of selection. Karlin derives a number of other intriguing results and his careful work deserves close attention. Like the work noted above, it casts doubt on the general applicability of the Fisher-Muller theory.

Reassortment Theories of Sexual Advantage

The Fisher-Muller theory emphasizes the potential power of recombination to produce one new genotype from many. In sharp contrast stand several rather more disparate theories which emphasize the power of recombination to produce

many new genotypes from a few. And whereas the Fisher-Muller theory postulates very limited standing genetic variation, these reassortment theories of sexual advantage, in common with the balance school of population genetics (Dobzhansky, 1955, 1970; Lewontin, 1974), postulate large amounts of selectively relevant genetic variation in natural populations.

The reassortment theories date directly back to Weismann (1891, 1892). (The relationship of the Fisher-Muller theory to Weismann's ideas is less direct than Muller, 1932, suggests, though it does bear some resemblance to Weismann's later work, 1904, in which he accepts the existence of mutation-like events.) In Weismann's view selection acts to perpetuate the best of the very large numbers of hereditary combinations produced by sexual crossing, so that as environments change species adapt in concert. Conversely:

> "all species with purely parthenogenetic reproduction are sure to die out; not, indeed, because of any failure in meeting the existing conditions of life, but because they are incapable of transforming themselves into new species, or, in fact, of adapting themselves to any new conditions"(Weismann, 1891, p. 298).

Later Weismann softened his view on the immutability of parthenogenetic species, but he still held that "their capability of transformation must be much smaller than in bisexual species" (Weismann, 1892, p. 166).

Contemporary reassortment theories stem primarily from early work by Darlington, Mather, and Dobzhansky, and to a lesser extent Wright. Darlington (1932, 1939, 1958) and Mather (1941 and later) emphasize the role of linkage in the controlled release of genetic variation, Darlington concentrating on the recombinational implications of various alternative breeding systems, Mather on a very special theory of the role of linkage, to be discussed in detail below. Dobzhansky (1951, 1955, 1959, 1970) stresses the purported role of Drosophila chromosomal inversions as instruments of adaptive recombination suppression. Wright's position (1931 and later) is a bit subtler and has had less influence. Recombination, he believes, underlies species potential for, but not necessarily species realization of, evolutionary advance (Wright, 1931 and later). All four authors share Weismann's basic conclusion, that in the long run sexual species outlast and outevolve asexual competitors because they are better able to tap existing hereditary variation and put it to use.

The reassortment theorists put forward two sorts of evidence or argument to support their hypotheses. On one hand they invoke experimental evidence that recombination generates a wide array of genotypes. Dobzhansky's views in particular have inspired a large number of experiments designed to demonstrate the recombinational generation of genetic variability from small numbers of wild-derived Drosophila chromosomes (Dobzhansky, 1946; Wallace et al., 1953; Spassky et al., 1958; Speiss, 1958, 1959; Dobzhansky et al., 1959; Krimbas, 1961; Speiss and Allen, 1961; Allen, 1966; Kosuda and Moriwaki, 1971; and see a related experiment by Mitchell, 1958). These experiments do demonstrate that recombination can generate large genetic variance for particular characteristics starting from single pairs of chromosomes. They do not, and this is important, establish the nature of the underlying genetic variation (Speiss and Allen, 1961; Lewontin, 1974, pp. 67-68).

On a more abstract level supporters of the reassortment theories often fall to calculating the very large numbers of possible genotypes that recombination among a moderate number of polymorphic loci might produce. For example, if n variable loci segregate for x alleles each, the number of possible haploid genotypes is x^n (Wright, 1932) and the number of possible diploid genotypes is $\left(\frac{x^2 + x}{2}\right)^n$, figures clearly enormous for any appreciable number of segregating loci. Weismann himself (1891, pp. 134-135) very early established this

tradition of argument by overwhelming calculation. It has since become virtually de rigueur to include in evolutionarily oriented genetics texts a numerical example of the power of sexual reproduction to generate immense numbers of genotypes. Almost always this takes the form of a small integer raised to an incomprehensible power. The implication, sometimes explicit, sometimes not, is that with so many genotypes at its disposal natural selection must be all the more effective in promoting adaptation to diverse and changing environments.

But even assuming that the reassortment theorists are correct in their inference that sexual reproduction can and does produce an almost boundless diversity of genotypes, diversity does not translate automatically into evolutionary advantage or advance. In a population that has evolved for some time in a constant environment exactly the opposite may be true. Well adapted genotypes may be at high frequency. Their erosion through recombination will lower the reproductive success of sexual individuals and the mean fitness of the population. The generation of diversity will be ill-adaptive per se. To make their theories work proponents of the reassortment theories of sexual advantage must hypothesize temporally changing environments or migration among geographically varied environments. Recombination among existing selected genotypes is a plausible evolutionary advantage only when organisms regularly encounter environments different from those of their parents or more distant progenitors. Even when environments change, different patterns of variation or heterogeniety may imply very different consequences for patterns of recombination (Mather, 1943; Thoday, 1953; Levins, 1965a, 1968), a topic examined in more detail below.

Finally, the consequences of recombination among a multitude of existing genotypes must depend very much on the (prevailing) nature of inter-locus interactions among alleles, just as the precise nature of these interactions is crucial to the Fisher-Muller theory. Wright (1931 and later) has emphasized the importance of this problem. Selective values at one locus may depend on alleles present at other loci in the same genome. Selection will tend to drive large panmictic populations to the most accessible well-adapted combinations, not necessarily the best. Should recombination subsequently throw up genotypes better adapted to prevailing conditions they will be swamped by recombination with common genotypes. Unless the recombinable components are advantageous separately as well as together (genetically additive in a loose sense), the best adapted combinations may never increase in frequency under individual selection. The primary evolutionary question becomes "whether there may not be, after all, some way in which there may be selection among the innumerable favorable possibilities provided by recombination among interacting genes" (Wright, 1965). Once again, sexual reproduction may ensure ample genetic variation, but it does not ensure that it can or will be put to use.

Like Wright, the other founders of the reassortment theories recognize and at times take pains to emphasize the dual nature of recombination, the fact that it tears apart well adapted genotypes as readily as it throws them together. But in science, as in politics, written words and social influence may not completely coincide. Casting aside the nuances, subtleties, and qualifications they may have attached to their hypotheses, the reassortment theorists, aided by theorists of the Fisher-Muller school, have projected a straightforward unambiguous conclusion to biologists at large, the conclusion that sex accelerates response to selection, thereby facilitating evolutionary change. This idea appears over and over, hidden and overt, in the general literature of biology. It crops up as an auxiliary assumption in a host of more specialized works on evolution and breeding systems. Most biologists believe that it is true.

Recombination and Rate of Response to Selection

Despite most biologists' uncritical acceptance of the notion that sex accelerates evolution, the idea has, until very recently, never been put to experimental test, never, that is, with one major exception. The exceptional experiment we owe to Carson (1958), who built his work to some extent on earlier experiments by Rasmuson (1954, 1955). Carson (1955a, 1955b, 1957) hypothesized that structural monomorphism in the chromosomes of marginal Drosophila populations promotes the formation of genetic novelties and therefore promotes more rapid response to selection. To test this idea he selected for motility, a complex behavioral trait, in populations of D. robusta, a species polymorphic for an extensive array of inversions involving most of its genome. Towards the central part of the D. robusta distribution individuals tend to be highly heterozygous for inversions. Towards the species margins inversion frequencies and inversion heterozygosity drop off sharply, so that most individuals are homozygous for standard chromosome sequences. Since inversion heterozygosity strongly suppresses recombination, recombination should be freer in marginal populations.

Carson selected for six generations on several separate lines, each derived from a single pair mating. Some parental pairs came from a central population, others from a marginal population. By the last two generations the marginal lines exceeded the central lines in mean response, leading Carson to this cautious interpretation:

> "The amount and speed of response to selection appears to be greater in lines which are structurally homozygous than those which are structurally heterozygous. The most likely cause of this difference is considered to be the very much smaller amount of recombination which is possible between polygene complexes in the sectionally heterozygous [central] lines."

Re-analysis of Carson's published data suggests that the marginal and central lines did not differ significantly in mean response. Neither set of lines is consistently higher in response and the difference between the mean responses is significant at the 10% level in only one generation, the fifth. Interestingly, the variance in response among the central (restricted recombination) lines is consistently greater than the variance in response among the marginal lines. Measured in terms of score achieved this is true in every generation.

Carson's data provide little support for his hypothesis, all the less taking into account the completely different geographic origins (and thus potentially very different gene pools) of his suppressed and recombining lines. Nevertheless, his experiment stood virtually alone for over a decade as the single direct test of the effect of recombination on speed of evolution, the single direct test of the reassortment theories. Evidently biologists were deeply predisposed to accept Carson's conclusions, however tenuous their factual base (for an apparent exception see Jain and Suneson, 1966). People felt no compelling need to repeat or extend his work.

Recently, a number of workers have retested the hypothesis that recombination speeds response to directional selection. McPhee and Robertson (1970) selected for high and low sternopleural bristle number, putatively a polygenic trait, in Drosophila melanogaster, using balancer chromosomes to suppress autosomal recombination in certain selection lines. In one experiment they selected for low bristle number, in a second they selected in both directions. In the first case they found a tendency for suppressed recombination to suppress response. In the second case suppressed recombination seemed to suppress response in high selected lines but had noticably less effect on low selected lines. Overall, on a transformed scale of measurement, the suppressed recombination lines

averaged only about 75% of the total response of the normally recombining controls. The results are not quite as clear-cut as they might first appear. McPhee and Robertson measure total response in terms of score achieved at the end of selection, when most of their lines have effectively plateaued, or ceased to respond. From their published graphs it appears that rates of response in the suppressed and normal lines were very similar until the suppressed lines began to plateau, at lower average levels of response.

I followed up McPhee and Robertson's work with a similar experiment using phototaxis mazes (Hadler, 1964) to select sixteen commonly derived D. melanogaster populations for positive phototaxis, another putatively polygenic trait. In some populations I suppressed autosomal recombination using balancer chromosomes, in others recombination proceeded normally. The responses of the suppressed recombination lines and their normal counterparts were indistinguishable, with one possible exception. As in Carson's work, the data hint that lines in which recombination was blocked exhibited more variable response. The primary result is clear. Sex had no detectable effect on mean rate of response to selection. This work is reported in detail elsewhere (Thompson, 1974, and submitted for publication).

Markow (1974, 1975) has conducted a series of experiments similar to my own. She too selected for phototaxis in several D. melanogaster populations, suppressing recombination in some, allowing normal recombination in others. Though her work parallels mine in many details, she draws the opposite conclusion. Certain combinations of balancers, she asserts, do suppress response to selection for positive or negative phototaxis, though in the majority of cases, recombination suppression seems to have no effect. Three factors make Markow's results difficult or impossible to interpret. First, she ran a single population to test each combination of balancers for selection in a given direction. Since variation among replicate lines in phototaxis selection experiments is very large (Thompson 1974, and submitted for publication), experiments without replication may give very misleading results. Secondly, her experiments included no controls to adequately distinguish the morphological effects of balancers from the effects of recombination per se, a distinction that proved to be important in my work. Finally, she initiated her experiments by mixing together many different populations of heterogeneous origin, a practice likely to introduce artificial linkage disequilibrium, profoundly complicating the interpretation of results (see below). Strictly speaking, Markow's results are compatible with my own, since she reports that suppression of autosomal recombination alone has no effect on response to selection for positive phototaxis.

Taken together, the experiments of Carson, McPhee and Robertson, and Markow, as well as my own experiments, do not provide a very satisfactory answer to the question "does recombination speed response to selection?" My work suggests that the answer is no. The others' work suggests the opposite conclusion but their data are not particularly convincing. This exhausts the experimental data on manipulated recombination and directional selection. But we can appeal these apparently conflicting results to another quite separate body of work, computer simulation studies of directional selection in multilocus systems with various degrees of linkage.

Computer Simulation Studies and the Reassortment Theories

Four sets of computer studies bear directly on our discussion. They all simulate the evolution under directional selection of many linked loci with alleles at intermediate frequencies. In an early study Fraser (1957) modeled the evolution of two chromosomes, each with three loci polymorphic for two alleles. We can summarize his results as follows: 1) The tighter the linkage,

the slower the rate of response to selection. 2) The smaller the population, the greater the effect of linkage. 3) The farther the chromosomes in the original population from the optimum genotype (the greater the initial negative linkage disequilibrium), the greater the effect of linkage. On the whole the effects of linkage were small unless linkage was very tight.

Martin and Cockerham (1960) followed up Fraser's work with a more extensive study on single chromosome systems with five or twenty loci. Most runs they initiated with random combinations of alleles at different loci (linkage equilibrium), but they initiated a few runs in complete negative linkage disequilibrium ("loaded repulsion") so that founding individuals were all of genotype 10101/01010 where 1 and 0 represent the favored and disfavored alleles at each locus. Like Fraser they found that initial negative linkage disequilibrium may drastically affect response, the tighter the linkage the slower the response. With initial linkage equilibrium, linkage effects were small but significant, the larger the number of loci and tighter the linkage the slower the response. In general smaller population size slowed response and exaggerated the effects of linkage.

Fraser and Martin and Cockerham simulated relatively small populations, ranging in effective size from four to fifty. Using a ten locus model, Young (1966) extended simulation to larger populations, effective size at least one hundred, with initial linkage equilibrium. Under these conditions linkage had very little effect on response. Unfortunately, the tightest linkage Young examined was only .05, a rather high minimum rate of recombination.

Probably the most extensive simulation studies of linkage and selection to date are those of Qureshi, Kempthorne and Hazel (1968) and Qureshi (1968). They studied a four chromosome 40 locus model with populations in initial linkage equilibrium. Restriction of recombination had negligible effect in the early generations of selection, but tended to slow down, or at least restrict, response in the long run. Again, linkage effects increased with decreasing population size. Qureshi et al. conclude that the inhibitory effect of small population size on rate of response appears to increase in geometric proportion to the tightness of linkage between loci. With moderately large populations (sixty-four individuals), linkage effects seem to be negligible for recombination rates of .05 or more.

A few more abstract simulation studies also merit attention. Latter (1966) simulated a two locus model and found that population size has a much larger proportionate effect on rate of response than linkage, the smaller the population, the smaller the average response. Hill and Robertson (1966), also studying a two locus system, found that over a wide range of parameters linkage effects may be adequately described by the term Nc where N is effective population size and c is recombination rate. Large population size compensates for tight linkage. Hill and Robertson also found that linkage has little effect on response in initial generations, but does slow response and the rate of approach to fixation in later generations. Robertson (1970) has extended their work to systems of many linked loci, showing that as the number of loci increases, so too will the inhibitaory effects of linkage on total selection response (the limits to selection), though the process tends toward a limit at a few dozen loci. Robertson concludes that the effects of linkage on directional selection for a trait determined by a moderate number of loci with intermediate gene frequencies and initial linkage equilibrium will be small, "much less," he says, "than I had expected and less than might be assumed from discussions of linkage in the literature.

Remarkably, reference to these simulation studies is virtually absent from the literature discussing the evolutionary role of sex (Felsenstein, 1974, does discuss Hill and Robertson's work in relation to the Fisher-Muller theory),

perhaps because they have been directed towards a practical problem, the role of recombination in agricultural breeding programs. Whatever the reason for their neglect, the computer studies suggest that two major factors should dominate the relationship between recombination and directional selection: 1) population size, and 2) the state of linkage equilibrium. These factors are also key to understanding the various derivative models of the Fisher-Muller theory (Karlin, 1973; Felsenstein, 1974).

The importance of population size for the reassortment theories is not difficult to grasp. Given a system involving many variable loci, populations of small to moderate size simply cannot harbor all possible genotypes simultaneously. Suppose, for example, that in a haploid ten locus system with initial gene frequencies all equal to 0.5, selection favors individuals of genotype 1111111111 (using the notation introduced above). If inter-locus allelic combinations are initially random (linkage equilibrium), the probability that any given organism will harbor the optimal combination is only $0.5^{10} = 9.72 \times 10^{-4}$. In small populations optimal combinations are unlikely to exist; the larger the number of loci involved and the smaller the frequencies of desirable alleles at each locus, the smaller the chance becomes. When optimal combinations must be produced through recombination, linkage impedes their production; the smaller the population size and tighter the linkage, the longer the average wait for recombinants and the slower the initiation of response to selection if response depends on the creation of new genotypes from existing genes.

Finite population size may influence total response (the limits of selection) as well as rate of response to selection. In tightly linked systems chromosomal combinations tend to behave as multiple alleles at a single locus. Selection operates to sort out existing chromosomes and drives the best towards fixation. Should the best chromosome happen to carry undesirable alleles these will be driven to fixation along with the rest unless recombination intervenes. The final response will not be the optimum possible response. In small populations random loss of desirable alleles during the course of selection will also reduce final response; the shorter the period of selection, the less probable this process becomes, but the more probable the fixation of undesirable alleles through association with good ones. Selection response becomes, in a sense, a race between recombination and genetic drift, a relationship that underlies the models of Hill and Robertson (1966) and Robertson (1970). In the context of a rather different selection model, Franklin and Lewontin (1970) note that finite population size itself determines the existence of an optimum recombination fraction.

Did finite population size influence the experimental results discussed above? Yes, almost certainly. Carson selected on populations of very small size, four pairs of parents per line per generation. We can ascribe his positive results, if they are real at all, directly to small population size. McPhee and Robertson selected on populations of effective size about ten. Their results too may be ascribed to finite population size. In fact, that is how they analyze them themselves (though they are concerned with limits to selection, not rate of response per se). Markow and I both selected on populations approaching the size at which Qureshi et al. found virtually no effect of reasonably loose linkage on response. I found that recombination has no effect on mean response. Markow's data are at least consistent with this assertion.

Sex, it appears, should speed response to selection, just as the reassortment theorists predict, but the effect should be significant only in very small populations, smaller, perhaps, than are likely to be the rule in nature. If this is the major function of sex, sex must play a limited role in evolution. But then why do so many species cling tenaciously to sexual reproduction? Are

there perhaps other advantages to sex associated with the second major factor found to influence the simulation results, linkage disequilibrium?

Linkage Disequilibrium and Mather's Polygene Theory

Linkage disequilibrium, non-random association of alleles across loci, may speed or slow response to selection, depending on its direction. Positive linkage disequilibrium, an excess of coupling combinations (11 and 00 for a two locus case), so that alleles influencing a trait in the same direction tend to be associated in the same chromosomes (or haploid genotypes), speeds response to selection by exaggerating genotypic variance within populations. Negative linkage disequilibrium, an excess of repulsion combinations (01 and 10), slows response to selection by depressing genotypic variance. Felsenstein (1965) proves these relationships rigorously for two haploid models and a more limited diploid model. And they are evident in Lewontin's (1964a) general formula for gene frequency change in deterministic two locus linked systems with discrete generations:

$$\Delta x_i = \left[\frac{x_i(1 - x_i)}{2} \frac{\delta \bar{w}}{\delta x_i} \pm RDW_{11} \right] \frac{1}{\bar{w}}$$

where x_i = frequency of the ith allele
$\bar{w}$ = mean fitness of population
R = recombination fraction
W_{11} = fitness of double heterozygote
D^{11} = linkage disequilibrium determinant

In the terminology introduced above D is $x_{11}x_{00} - x_{10}x_{01}$ where the x's represent frequencies of the coupling and repulsion combinations. Note that when D = 0 (linkage equilibruum), the term RDW_{11} drops out of the equation and recombination does not effect response. This suggests *a priori* that only in the presence of linkage disequilibrium (initial or otherwise) will sex influence selection in very large populations, a point confirmed by Karlin (1973) and by Felsenstein (1974) who notes that recombination can influence the gene pool *only* by breaking down linkage disequilibrium.

Mather (1941, 1942, 1943) has proposed a very influential model for the function of sex in natural populations. His argument relies decisively on interaction between recombination and linkage disequilibrium; it rests on three major premises: (1) Quantitative traits are determined by many loci of small, equal, and additive effect dispersed throughout the genome. (2) These loci exhibit intermediate gene frequencies (placing Mather squarely in the reassortment camp). (3) In the short term environments fluctuate erratically and often abruptly, but medium term selection favors intermediate phenotypes for most measurable characteristics. Over time, intermediate optimum phenotypes may change in response to long term directional environmental changes.

Populations, the argument goes, face conflicting evolutionary requirements. They must preserve their capacity for long term change without responding too strongly to short term selective pressures. Mather suggests that linkage resolves this contradiction in the following way. In polygenic systems many different genotypes may determine any given phenotype. For intermediate optima selection favors chromosomes with balanced combinations of alleles adding to or subtracting from a particular trait. Combinations like 111000 or 101010 are favored over combinations like 001000 or 111110. Furthermore, selection will favor combinations that minimize the probability of creating unbalanced chromosomes through recombination. Chromosome pairs like 101010 and 010101 are better

balanced than pairs like 111000 and 000111. In the first case five recombination events are required to produce the extreme allelic combinations, in the second only one. Populations will strike a balance between the proliferation of well balanced combinations through selection and their erosion through recombination; the tighter the linkage, the greater the predominance of balanced combinations, and the less the flexibility of the population in response to directional selection.

Mather's polygene theory predicts the generation of substantial negative linkage disequilibrium in natural populations. Negative linkage disequilibrium slows directional selection. Recombination disrupts linkage disequilibrium. Therefore in Mather's model sex should accelerate response to directional selection for traits that have been under selection for intermediate optima. This is the source of Mather's very large contribution to the notion that sex accelerates evolution (see, for example, Carson, 1958), but the fact that the model depends so crucially on negative linkage disequilibrium is almost always overlooked.

Population geneticists have raised two serious objections to Mather's model (Wright, 1945; Lewontin, 1964b). First, it does not provide for the long term maintenance of polymorphism at individual loci. Eventually populations will go to fixation for single well balanced combinations; evolution will stall. In addition, to maintain balanced combinations at significant frequencies recombination between loci must be very small, on the order of magnitude of the selection coefficients associated with individual loci. Since the model predicts many loci, selection coefficients at each must be small and the linkage between loci would have to be improbably tight. Mather (1953) answered these objections by appealing to selection experiments showing periods of "accelerated response," in which populations that have failed to respond for a number of generations renew their advance, often abruptly and for a limited period. These responses Mather attributes to rare recombinations among closely linked loci in balanced polygenic systems. The facts do not support this interpretation.

Mather's own early experiments (Mather, 1941) may serve as an example. He selected D. melanogaster populations for high and low abdominal bristle number. Response was uneven, alternating between periods of little or no progress and periods of rapid advance. But the selected populations were very small, two parents of each sex per generation. In tiny populations recombinational effects on selection do not necessarily imply linkage, let alone linkage disequilibrium. Even should substantial linkage disequilibrium exist in small populations, it may reflect the random processes inherent in populations of finite size (Sved, 1969, 1971; Hill and Robertson, 1968; Ohta and Kimura, 1969).

Virtually all other reports of striking accelerated response fit the same pattern (Payne, 1920; Sismandis, 1942; Mather and Harrison, 1949; Fraser et al., 1965; Scowcroft, 1966; Hosgood, MacBean and Parsons, 1968; MacBean, McKenzie and Parsons, 1971; Thoday and Boam, 1961; Thoday, Gibson and Spickett, 1964; Spickett and Thoday, 1966). In most cases population size is very small, five pairs of parents per generation or fewer. In addition, most accelerated response experiments have involved base populations in some sense heterogeneous in origin. Mather, for example, selected on flies derived from a cross between laboratory stocks of very different origin, introducing another very real potential source of linkage disequilibrium. The experiments of MacBean et al. and Thoday and his co-workers are telling in this respect. They present credible evidence that certain observed accelerated responses do in fact stem from recombination between closely linked "loci". But in each case the loci involved contribute a sizable portion of total selection response. They are loci of major effect, not polygenes in Mather's sense. And even then Thoday et al. are forced to postulate that they built negative linkage disequilibrium into their

base populations. Finally, it is important to note that many accelerated responses may have no relation to recombination among linked loci. Fraser and Hansche (1964) and Wright (1969) present alternative models for such effects, and Fraser et al. (1965) present evidence that accelerated responses during selection for high scuteller bristle number (the trait employed in many of the experiments above) may not be directly due to artificial selection at all.

Linkage Disequilibrium in Nature

Despite the absence of convincing evidence supporting Mather's hypothesis, interest in selection models that generate linkage disequilibrium has recently grown. This reflects Lewontin and Kojima's (1960) demonstration that epistatic interactions between loci may lead to stable linkage disequilibrium and the subsequent demonstration by many authors that selection for intermediate optimum phenotypes in additive multi-locus systems may lead to the build up of considerable long term negative linkage disequilibrium (Lewontin, 1964b; Fraser, Miller and Burnell, 1965; Wills, Crenshaw and Vitale, 1970; Franklin and Lewontin, 1970). These models, like Mather's, require tight linkage. Now, with the discovery of very high levels of electrophoretically detectable protein variation, close linkage of many polymorphic loci has become a tenable proposition (discussion in Lewontin, 1974).

At this writing direct evidence for widespread linkage disequilibrium in natural populations is sparse and limited for the most part to special circumstances. Many investigators have detected linkage disequilibrium involving dipteran inversion polymorphisms (Levitan, 1955, 1958, 1973a, 1973b; Levitan and Salzano, 1959; Stalker, 1960, 1964; Brncic, 1961; Mather, 1963; Sperlich and Feuerbach-Mravlag, 1969, 1974; Martin, 1965; Prakash and Lewontin, 1968, 1971; Prakash and Merritt, 1972; Prakash, 1974; Nair and Brncic, 1971; Kojima, Gillespie and Tobari, 1970; Mukai, Mettler and Chigusa, 1971; Mukai, Watanabe and Yamaguchi, 1974; Langley, Tobari and Kojima, 1974). Others have reported inter-locus disequilibrium in self-fertilizing plants (Allard et al., 1972), in predominantly parthenogenetic Daphnia (Hebert, 1974), and among very tightly linked and perhaps functionally and phylogenetically related loci in Drosophila (Roberts and Baker, 1973; Baker, 1975). In addition, Clarke (1974) has recently called attention to older studies on flowering plants, snails, and butterflies which indicate substantial disequilibrium between closely linked loci controlling related morphological characters,

A few investigators have detected occasional cases of linkage disequilibrium in regularly outbreeding organisms among loci that are fairly widely spaced and not obviously functionally related (Zouros and Krimbas, 1973; Zouros, et al., 1974; Franklin, 1973; Charlesworth and Charlesworth, 1973; Birley, 1974). By chance, the Charlesworths studied Ives' (1970) Amherst D. melanogaster population, the same population used in my own studies on recombination and selection response (Thompson, 1974, and submitted for publication). Using electrophoretic techniques they searched for disequilibrium among five third chromosome loci. Among the ten possible two locus interactions, two proved to be significant at the 5% level. In an unrelated cage population two different interactions proved to be significant at the 1% level. Internal consistencies in the data suggest that some of the disequilibria, though small, may be real.

The available scant evidence suggests that, except in a few special cases, linkage disequilibrium in natural populations is small, small enough certainly to have no more than a trivial effect on response to selection. And we know almost nothing about linkage disequilibrium among loci determining quantitative traits. We can only infer its presence or absence from the results of recombination and selection experiments (McPhee and Robertson, 1970), a risky

venture in the absence of independent knowledge concerning the number of loci segregating, their linkage relationships, the relative magnitudes of their effects, and their modes of interaction.

Here then we have a real mystery, a real gap in evolutionary theory. Sex should speed the evolution of small populations and populations in negative linkage disequilibrium, but most populations most of the time must be rather too large to benefit from the population size effect, and the evidence outlined above suggests that standing linkage disequilibrium in most populations is small or absent. In addition biparental reproduction suffers serious shortcomings as a reproductive mechanism (Maynard Smith, 1971a, 1971b). Parthenogenetic females producing female progeny will in general be twice as fit as sexual females producing equal numbers of male and female offspring, and parthenogenetic populations will reproduce twice as quickly as their sexual counterparts. Furthermore, biparental reproduction requires the union of gametes from two individuals, and often a temporary union of the individuals themselves. The necessity to juxtapose gametes has led to the evolution of elaborate morphological and behavioral characteristics in a wide array of species. And many secondary sexual characteristics must, as Darwin (1901, p. 299) noted long ago, seriously hinder adaptation to "the general conditions of life". Asexual reproduction abolishes the necessity for gametic union opening the way to evolution unemcumbered by special adaptations for sexual search and attraction. Yet sex persists widely in nature. Why might this be so?

The Mixing-of-Populations Model of Sexual Advantage

The models considered so far postulate populations evolving in isolation, a situation that must be uncommon in nature. Suppose that selection in local populations favors different inter-locus combinations of alleles. Should separate populations then exchange migrants or combine, the resulting populations will be in linkage disequilibrium (Prout, in appendix to Mitton and Koehn, 1973; Nei and Li, 1973; Li and Nei, 1974). If selection in the amalgamated populations favors gametic combinations that pre-exist in the component populations, linkage disequilibrium will be effectively positive, and tight linkage will facilitate adaptation in the new populations. Sex will be disadvantageous. This must often be the case when migration occurs into or among well adapted local populations, or when migrants of superior genotype move into local populations where the environment has recently shifted. But if the environments of new populations favor combinations that do not exist in the component populations, linkage disequilibrium will be effectively negative, linkage will slow down adaptation, and sex will be advantageous (see Dawson, 1970, for an experimental model analogous to this situation).

Sturtevant and Mather first proposed the mixing-of-populations model in 1938 and Maynard Smith (1968, 1971a, 1971b, 1974) has proposed it again more recently. It clearly falls among the reassortment theories, postulating large amounts of standing genetic variation. But the variation need not take the form of intermediate gene frequencies in local populations; it may take the form of fixation for different alleles in different populations, a situation close to that hypothesized by Wright. Wright himself (1949) seems to favor the idea that migration will lead to positive linkage disequilibrium, so that linkage will maintain the integrity of "adaptive complexes" immediately following immigration or hybridization. Recombination between populations must also play a role in the third phase of Wright's (1970) shifting-balance model of evolution, the phase of inter-demic selection and the creation of new adaptive types at the borders between successful demes. But since recombination would work to destroy the beneficial combinations of each deme as well as combine them together, the role of sex in the process is not at all clear.

Mather (1943) eventually abandoned the mixing-of-populations model on the grounds that it represented too special a case to be of much importance in nature. Crow and Kimura (1969) have recently echoed this sentiment. How commonly the model applies must vary tremendously from species to species, depending on population structure and the spatial and temporal heterogeneity of environments. One example will illustrate the complexities that may arise. Theoretical work by Nei and Li (1973; Li and Nei, 1974) indicates that subdivided populations in heterogeneous environments with moderate amounts of migration may exhibit stable linkage disequilibrium, even in the absence of epistatic interactions among the loci involved. Because each subdivision has adapted to a fixed local environment, migrants' genotypes are maladaptive, linkage disequilibrium is positive, and sex within subdivisions will slow down the elimination of maladapted immigrant alleles by shuffling them into the local genotype. But should local environments be shifting rather than fixed, so that recombination among local and migrant genotypes often produces adaptively superior combinations, linkage equilibrium will be effectively negative and sex will be advantageous to many populations.

Seen in this light we may reinterpret Carson's (1955a, 1955b, 1958, 1959) theory of evolution in marginal populations. He argued that in such populations recombination facilitates the formation of novel genotypes adapted to stringent environments; the more recombination, the faster the adaptation. The arguments above expose the difficulties inherent in this view. But suppose, as Lewontin (1974, p. 151) argues, that marginal habitats are characterized by temporal instability, and that marginal populations are temporally unstable as well, fragmenting and reamalgamating over time. If selective pressures vary from sub-population to sub-population, populations may often be in negative linkage disequilibrium with regard to environments at hand and sexual reproduction may, as Carson proposes, play an important role in speeding adaptive response.

This argument may be extended to many or most "weedy" or "fugative" species which populate impermanent or erratically shifting habitats. For example, in temperate climes D. melanogaster appears to overwinter as small populations confined to a few restricted sites. Each spring overwintering survivors emerge to build up local populations which spread and intermingle over the course of the summer reproductive season, a process reflected in a decline in the allelism of lethals in local populations as the season progresses (Ives, 1970; Franklin, 1973). If the mingling populations reflect selection in significantly different environments, and if the environments of their descendants are often significantly different from their own, sex may facilitate adaptation. Quantitative arguments by Maynard Smith (1971b) suggest that "significantly different" in this case means very different indeed, with the correlation between environmental attributes relating to different loci changing sign from generation to generation. The extent to which such processes are important in nature will depend very much on the interaction of environmental patterns and individual physiological flexibility within species. If, for example, the environments of some weedy species are effectively the same generation after generation despite constant shifts of location, Stebbins (1958) is correct to argue that sex will be detrimental to adaptation.

Sex as a Mechanism for Damping Selection Response

Implicit in this discussion so far has been the assumption that genetic change is good in itself, the faster the better. But the mixing-of-populations model suggests, as Mather (1943) and Thoday (1953) pointed out some time ago, that genetic change will be beneficial only in response to certain patterns of

environmental change. Levins (1965a, 1968) has developed this theme. Using a computer to simulate the behavior of a deterministic two-locus system with additive interactions in the face of fluctuating environments, he demonstrates that optimum recombination levels depend on the periodicity or serial autocorrelation of successive environments. When environment fluctuates rapidly, with a period short compared to generation time, complete linkage (no sex) maximizes population fitness over time. From the point of view of the population the environment is unpredictable (or physiologically averaged) and it is better not to evolve at all. When the period of environmental fluctuation is long compared to generation time, intermediate recombination levels may maximize fitness over time. Presumably, as the period of fluctuation becomes very long the population will see the environment again as effectively constant and the optimum recombination rate will again be zero. Sex facilitates evolution in response to environmental fluctuations of intermediate length. This result rests on Levins' use of strictly additive fitnesses. Had he used multiplicative fitnesses linkage would have had no effect. It would be interesting to repeat this work introducing finite population size, multiple loci, and other fitness relationships.

Note that populations selected in different points in time, as well as space, may often hybridize (plants with variable seed dormancy, animals with resting eggs, plants and animals from different year classes), suggesting the utility of a synthesis combining the mixing-of-populations and the Levins models. Levins himself (1965b) suggests that migration serves the evolutionary role of damping genetic response to local environmental perturbation. Sex, by scrambling incoming genes with the local genome, should delay their early elimination and facilitate this process.

My data (Thompson,1974, and submitted for publication) and Carson's data (1958) suggest, and, it must be emphasized, merely suggest, that suppression of recombination increases variation in response among populations subjected to directional selection. By inference, sex should decrease variation in response among replicate populations under selection. If this phenomenon is real, we may attribute it directly to finite population size. In infinite populations with no recombination selection will (assuming no complex interactions) pick out the best gametic combination and raise its frequency to fixation. There will be no variation in response among replicate populations. But in finite populations the best existing gamete will vary from replicate to replicate, so that replicates of asexual populations will vary considerably, both in speed of response (which will be proportional to the difference in fitness between the best existing gamete and the population mean) and level of final response.

Best existing gametes do not limit selection response in finite sexual populations. Sexual populations may generate new more highly fit combinations, though these may be torn apart in turn by subsequent bouts of recombination. In these populations arrays of alleles, or at least arrays of genotypic combinations, dominate response to selection. And allelic arrays must be similar from replicate to replicate, much more similar than the near-unique genotypic combinations that dominate response in finite asexual populations. Consequently, recombination should homogenize response among replicates at the same time it promotes variation within replicates. Sex tends to generate diversity within populations, but it should also diminish variation among commonly derived finite populations under directional selection.

What role might this phenomenon play in evolution? If inter-demic selection is important and often favors extreme responses to selection, only those populations with high or low mean response may survive to perpetuate species. Selection among species would favor the erratic collective response of groups of asexual populations. This appears unlikely. Turning the argument around,

perhaps sex benefits species not by speeding response to selection, but by moderating its course, so that more populations track environmental change efficiently, straying into neither excessive nor insufficient response. At the inter-population level sex damps response to environmental change. In effect this turns Mather's (1943) theory upside down. He argued that linkage, the negation of sex at the chromosome level, moderates response to selection within populations. I suggest that linkage exaggerates the range of response among populations. This hypothesis depends crucially on limited population size, and on the assumption that constellations of populations evolve in something approaching mutual isolation, conditions that do not apply to many species in nature.

But work by several authors (Lewontin and Kojima, 1960; Felsenstein, 1965; Bodmer and Felsenstein, 1967) suggests a role of more general significance for sex in large natural populations. Using various models they show that directional selection generates linkage disequilibrium in the presence of epistatic interactions among loci. The direction of the linkage disequilibrium, positive or negative, depends directly on the sign of the epistatic interaction, so that positive epistasis leads to positive linkage disequilibrium, negative epistasis to negative linkage disequilibrium. As noted above (see the section on Mather's polygene theory), positive linkage disequilibrium speeds response to selection while negative linkage disequilibrium has the opposite effect. By disrupting linkage disequilibrium, recombination tends to counter these effects.

I suggest that in nature environmental changes often confer great selective advantage on certain combinations of alleles among polymorphic loci previously independent in their effects on fitness. In other words, fluctuations in environment often lead to positive epistasis. If this phenomenon occurs regularly, directional selection will generate positive linkage disequilibrium,which in turn will hasten evolutionary response. Recombination, countering this trend, will tend to slow response, lessening reaction to environmental change. The key point is that positive fitness contributions by loci in combination be greater than the assumption of complete independence between loci would suggest. How much greater? For two locus haploid systems with discrete generations, recombination will slow response to selection when loci show supermultiplicative effects on fitness (Eshel and Feldman, 1970; Karlin, 1973; and see the discussion of the Fisher-Muller theory at the beginning of this paper).

Noting that recombination will slow selection response in some circumstances, Eshel and Feldman (1970) suggest that sex facilitates evolution in changing environments by "prolonging the polymorphic state," or, as Eshel (1971) restates their conclusion, by curbing "too-rapid genetic response to irregular and temporal environmental changes". They state this suggestion in the context of the Fisher-Muller model (evolution through the spread and combination of new or previously rare mutations) but I believe it fits the premises of the reassortment theories just as well. Sex, I suggest, generally retards change in gene and genotype frequencies in the face of short term environmental change. It does not accelerate evolution, it slows evolution down. Should this prove true, the negation of Mather's hypothesis proceeds a step further. Linkage, Mather's moderating factor, should exaggerate selection response, because populations under selection will show transient positive linkage disequilibrium, not the more or less permanent negative linkage disequilibrium that Mather hypothesized.

The hypothesis that sex moderates selection response by mitigating a spontaneous tendency towards positive linkage disequilibrium helps to resolve certain difficulties that afflict some of the earlier reassortment theories of recombination and sex. For example, many theories asserting that sex accelerates evolution depend in the last analysis on the hypothesized presence of negative

linkage disequilibrium in natural populations, a hypothesis for which there is very little evidence. I suggest, in contrast, that positive linkage disequilibrium develops as a largely transitory phenomenon in populations under directional selection, and that sex functions precisely to minimize its development, a notion compatible with the data from natural and experimental populations. In addition, the present hypothesis applies to large populations. It does not, as many reassortment theories do, require unrealistically small population sizes. Finally, it helps circumvent two major difficulties confronting the mixing-of-populations hypothesis, the necessity for continual migration among or amalgamation between separate local populations, and the concomitant necessity for comparatively finely balanced relationships among selective forces in the environments involved. Because, according to the hypothesis that sex counters the effects of positive epistasis, sex plays its main role within local populations.

The notion that sex serves primarily to slow response to selection is a venerable but neglected concept. It formed the basis for Charles Darwin's later views on the evolutionary function of sex (De Beer, 1960b, p. 164; Olby, 1966). Darwin saw in sex a mechanism for quashing over-strong response to local and short-term selection. Crossbreeding, he came to believe, blends large variations out of existence so that only small recurring variations appearing in many individuals accumulate in species. For Darwin the main role of sex is not to generate variability; it is to ensure a gradual, uniform,adaptive response to selection in the face of environmental heterogeneity. The ideas discussed above threaten to bring the discussion of sex back around full circle, to a proposal, however poorly grounded in its original form, that predates Weismann.

I noted that we have failed to carry Weismann's work through to the end. We have failed to elucidate in a fundamental way the role of sex in evolution. Perhaps the reasons for this are now more clear. The simplest implicit hypothesis of the reassortment theories, that sex speeds response to directional selection, will hold true only for limited circumstances, circumstances likely to prove uncommon in nature. It is not difficult to conjure alternative theories of sexual advantage, but it is very difficult to test the assumptions on which these theories are based. The Fisher-Muller theory, for example, has been ably and subtly developed over the years, most recently by Karlin (1973) and Felsenstein (1974). But the assumption on which the theory is based, the notion that evolution proceeds primarily through the rise and spread of new or previously rare mutations, may have no basis in fact. A satisfactory theory of sexual reproduction will require more understanding than we now possess concerning the precise nature of adaptive genetic variation, the effective patterns of environment which organisms encounter, and the role of inter-demic selection in evolution.

The last factor deserves special comment. As noted before, Williams (1966, 1975) and others staunchly maintain that the maintenance of sex in populations should be interpreted without resort to models requiring group selection. The models discussed in this paper all imply group selection, some more openly than others. They neglect individual selection and they do not in themselves explain what maintains sex in populations potentially or actually polymorphic for its presence or absence. Given the limited question "does sex accelerate evolution?", this issue is not especially important. Given the broader question "why does sex survive in species?", it may be critical.

Another point neglected in most discussions of sex to date merits close attention. I have implicitly assumed that sexual and asexual populations compete in all other respects on equal terms, that they are born full blown into the world with equal standing genetic variation. This accurately reflects my own experimental design (Thompson, 1974) but it may not reproduce so faithfully

the realities of nature. Asexual populations must often be genetically impoverished, particularly when they descend from small numbers of individuals, a point crucial to the arguments of Williams and Mitton (1973) and the crux of a recent polemic concerning an altogether different model for the role of sex in nature (Thoday, 1974; Roughgarden, 1974).

Potential genetic impoverishment may profoundly complicate analysis of the role of sex in evolution. Maynard Smith (1975) asserts, for example, that asexual populations will ordinarily respond to selection through the proliferation of single clones representing the fittest available genotype in each population. This would wipe out genetic variance, not only for characters under selection, but for all other characters as well, effectively eliminating the possibility of further evolutionary change in the absence of new mutation. Williams (1975, p. 151) argues along similar lines that asexual populations will come to harbor one or at most a few genotypes, greatly restricting potential for evolutionary change. If the absence of sex does drastically limit genetic variation in species, sex must in the long run accelerate evolution, but in a trivial manner, and a manner divorced from the immediate arguments of the Fisher-Muller school and the reassortment theorists.

Limited but compelling evidence from asexual species apparently saves the argument from this ignominious end. Many asexual "species" do show substantial genetic variation, both among individuals within populations and among populations (Suomalainen and Saura, 1973; Solbrig and Simpson, 1974; Lokki et al., 1975; and references in de Wet and Stalker, 1974, and Williams, 1975, p. 160). Evidently, the absence of sex does not spell doom to the raw material of natural selection. It just introduces another factor, one of many, that restricts variation. Perhaps sex speeds evolution on one hand by promoting the diversification of genotypes and slows it down on the other through the mechanisms suggested above, the relative strength of each effect depending on population size and structure.

By approaching sex from the other side, by studying patterns of sexual systems in nature, we might hope to infer something about sex itself. This is a hazardous endeavor. For instance, many organisms switch from asexual to sexual reproduction when they face major environmental change (Ghiselin, 1974; Williams, 1975). Does sex in these cases facilitate faster genetic adaptation to new environments? Or does it curb too rapid adaptation to conditions extreme and, from the standpoint of later generations, temporary and passing? Neither hypothesis particularly excels or suffers at the hands of the accumulated data of natural history. The facts do not force the issue, and taken alone, I suspect they never will.

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