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PERSPECTIVE: THE THEORIES OF FISHER AND WRIGHT IN THE CONTEXT OF METAPOPULATIONS: WHEN NATURE DOES MANY SMALL EXPERIMENTS

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Abstract.—We critically review the two major theories of adaptive evolution developed early in this century, Wright's shifting balance theory and Fisher's large population size theory, in light of novel findings from field observations, laboratory experiments, and theoretical research conducted over the past 15 years. Ecological studies of metapopulations have established that the processes of local extinction and colonization of demes are relatively common in natural populations of many species and theoretical population genetic models have shown that these ecological processes have genetic consequences within and among local demes. Within demes, random genetic drift converts nonadditive genetic variance into additive genetic variance, increasing, rather than limiting, the potential for adaptation to local environments. For this reason, the genetic differences that arise by drift among demes, can be augmented by local selection. The resulting adaptive differences in gene combinations potentially contribute to the genetic origin of new species. These and other recent findings were not discussed by either Wright or Fisher. For example, although Wright emphasized epistatic genetic variance, he did not discuss the conversion process. Similarly, Fisher did not discuss how the average additive effect of a gene varies among demes across a metapopulation whenever there is epistasis. We discuss the implications of such recent findings for the Wright-Fisher controversy and identify some critical open questions that require additional empirical and theoretical study.

Key words.—Average effect, conversion, epistasis, Fisher, interdemic selection, metapopulation, shifting balance, variance components, Wright.

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Two major theories of adaptive evolution were developed early in this century: Wright's shifting balance theory (SBT) and Fisher's large population size theory (LST). Although the mathematical details of these theories are largely in agreement, the conceptual emphases of Wright and Fisher were so different (Table 1) that where and how to apply the theories to the natural world has been and continues to be a source of controversy. In a recent paper, Coyne et al. (1997), echoing the early group selection literature, advocated Occam's razor (e.g., Williams 1966) as grounds for dismissing the SBT. They argued (p. 634) that "there are few empirical observations explained better by Wright's three-phase mechanism than by simple mass selection" and concluded that "it seems unreasonable to consider the shifting balance process as an important explanation for the evolution of adaptations." We consider this pronouncement to be premature. Coyne et al. (1997) considered as empirical evidence for Wright's SBT only phase III peak shifts demonstrated in nature. In doing so, they ignored many novel findings over the past 15 years from field observations, laboratory experiments, and theoretical research that have enriched both theories, especially Wright's. In this paper, we offer a synthetic perspective on the two theories in light of recent research rather than a point-by-point critique of Coyne et al. (1997).

Field studies in plants (Stevens et al. 1995; Kelly 1996, 1997) and in insects (Frank 1985; Breden and Wade 1989; Herre 1993, 1995; McCauley 1994; Wade 1994) have demonstrated the existence of intergroup selection in nature. These studies span population genetic structures ranging from full- and half-sib families (Frank 1985; Breden and Wade 1989; Herre 1993, 1995; Wade 1994) to neighborhoods (Kelly 1996) to local demes (Stevens et al. 1995; Kelly 1997). The mechanisms of intergroup selection include both differential extinction and proliferation of groups. The phenotypes investigated in these studies were diverse, ranging from sex ratio and cannibalism rates to seed set and leaf areas. There

TABLE 1. The fundamental differences in emphasis that underlie the Wright-Fisher controversy.

	Wright	Fisher
Central problem of evolutionary theory	Origin of adaptive novelty in a constantly changing environment	Refinement of existing adaptation in a stable or slowly changing environment
Major processes of evolutionary change	Combination of local natural selection, random genetic drift, migration, and interdemic selection	Mutation and natural selection
Ecological context of evolution	Small, subdivided populations	Large, panmictic populations
Genetic basis of evolutionary change	Epistasis and pleiotropy; context-dependence of allelic effects	Additive genetic effects; context-independence of allelic effects
Process of speciation	Inevitable by-product of local adaptation in epistatic systems	Disruptive or locally divergent selection

is also strong empirical evidence that the spread of human agriculture arose via a process of demic diffusion (Wijsman and Cavalli-Sforza 1984; Klein 1990; Sokal et al. 1991). Although none of these field studies measuring intergroup selection addressed the underlying genetics of the traits, we view them as empirical evidence supporting the SBT, whereas none are cited by Coyne et al. (1997).

Goodnight and Stevens (1997) reviewed laboratory experiments demonstrating the efficacy of intergroup selection for increasing and decreasing leaf area in the cress *Arabidopsis thaliana* (Goodnight 1985), lytic capability in the bacterium *Escherischia coli* (Chao and Levin 1981), and egg laying rates in domestic chickens (Craig and Muir 1996; Muir 1996). In the latter study, intergroup selection was able to achieve a 30% increase where long-term mass selection had failed. In flour beetles, *Tribolium* spp., artificial interdemic selection has been shown to be effective in changing mean fitness (Wade 1977, 1982, 1984; McCauley and Wade 1980; Wade and McCauley 1980, 1984; Wade and Griesemer 1998), migration rates (Craig 1982), cannibalism rates (Wade 1980a), and competitive ability (Wade 1980b, 1988, 1990; Goodnight 1990). Genetic studies of cannibalism in *T. confusum* do indicate the existence of multiple selective peaks (Stevens 1994), and genetic studies of fitness in *T. castaneum* (Wade 1985) do reveal epistasis. Phase III of the SBT, interdemic selection by differential migration, has been shown to be an effective force for changing mean deme fitnesses in laboratory metapopulations with degrees of population genetic subdivision comparable to those observed for many species in nature (Wade and Goodnight 1991; Wade 1996, unpubl.; Wade and Griesemer 1998). The laboratory metapopulations permit us to "calibrate" the population genetic structures and intergroup selective processes observed in natural populations of other arthropods (Wade and Breden 1986; McCauley 1987, 1989, 1991, 1993, 1994; McCauley et al. 1988; Olivieri et al. 1990; Whitlock 1992, 1994; Wade 1994; Herre 1995; Smith and Hagen 1996; Ingvarsson and Olsson 1997; Ingvarsson et al. 1997) and plants (McCauley et al. 1995; Stevens et al. 1995; Kelly 1996, 1997). These studies have rekindled interest in and controversy over the novel evolutionary properties of metapopulations, an ecological context conforming a priori more to Wright's theory than to Fisher's.

Complementing these empirical studies are theoretical investigations of the unique ecological and genetical processes of metapopulations (reviewed in McCauley 1989, 1991, 1993, 1995; Barton and Whitlock 1997; Milkman 1997). Local extinction and colonization create an age structure or demography of demes that can enhance or diminish the opportunity for interdemic selection (Slatkin 1985; Wade and McCauley 1988; Whitlock and McCauley 1990; Whitlock et al. 1993; Barton and Whitlock 1997). Colonizing propagules (the "new-born" age-class of demes in a metapopulation), especially when kin structured, can exert a dominant influence on metapopulation genetic structure in circumstances that appear to be common in nature (McCauley et al. 1988; Wade and McCauley 1988; Whitlock and McCauley 1990; McCauley 1991, 1993, 1995; Whitlock 1992, 1995; Whitlock et al. 1993; Wade et al. 1994; Barton and Whitlock 1997). Wright asserted that extinction with recolonization was "the most favorable situation for saddle crossing to operate" by random drift. Because demic age structure can magnify the genetic effects of random drift, these effects in toto clearly support a role for the SBT in adaptive evolution.

Although additive genetic variance governs the rate of adaptive evolution in both the LST and SBT, the role accorded to the epistatic genetic variance differs significantly between the theories (Wade 1992, 1996). Our understanding of the relationship between the additive and nonadditive components of genetic variance has been profoundly changed by recent theoretical developments (Tachida and Cockerham 1987; Goodnight 1987, 1988, 1989, 1995; Cockerham and Tachida 1988; Whitlock et al. 1993; Cheverud and Routman 1995a,b; Whitlock 1995). In almost all evolutionary discussion, the additive and epistatic components of genetic variation are considered separate and distinct entities, each playing a different role in the adaptive process. Most often, strictly additive models with no epistasis are investigated. Recent theory has shown that the additive and epistatic components of genetic variation are not fixed entities that can be discussed cogently in isolation from one another in the context of drift and small populations. Random genetic drift and natural selection convert epistatic to additive genetic variance within small populations (Goodnight 1987, 1988, 1995; Tachida and Cockerham 1987, 1989; Cockerham and Tachida 1988; Wade 1992; Whitlock et al. 1993; Cheverud and Routman 1995a,b; Whitlock, unpubl. ms.; Fenster et al. 1997). Reciprocally, migration between populations converts additive back to epistatic variance (Whitlock et al. 1993). It is well known that narrow-sense heritability and the additive genetic variance

change with gene frequency. It is less widely known that the estimated additive effect of a gene and its contribution to the additive variance change whenever the frequencies of its epistatic partners change (Goodnight 1987, 1988, 1995; Wade 1992, 1996; Cheverud and Routman 1995a,b; Toquenaga and Wade 1996; Wade and Fay, unpubl.). Furthermore, with genotype-by-environment interaction, the components of genetic variance change with changes in the environment. The epistatic component of genetic variance has been shown to increase in extreme environments (Jinks et al. 1973; Hoffmann and Parsons 1991; Blows and Sokolowski 1995).

Just as fixing one factor in a large, factorial design permits the effects of other factors to be explored more effectively, fixing one gene permits the effects of its epistatic partners to be explored more effectively by natural selection. Also, just as pooling the results of several small, independent experiments can provide an effective way of converging on an optimal solution, Wright's SBT provides a mechanism for the biased pooling of local adaptive events in metapopulations. This is the essence of our title metaphor, nature's many small experiments. With epistasis, the effect of an allele in one deme can be different from its effects in another because random genetic drift and local selection can fix different alleles in the family of genes with which it interacts. Differential migration, out from demes with high mean fitness and into those with lower mean fitness, is a mechanism for pooling these many small genetic experiments with greater weight being given to the better solutions.

In the analysis of Coyne et al. (1997, p. 653), an advantageous gene "can spread easily across geographic barriers," whereas gene combinations "may be trapped by local barriers to gene flow." In the SBT with epistasis, the magnitude and sign of the average additive effect of a gene will vary from population to population. An advantageous gene is *not* advantageous everywhere; it is sensitive to variations in the genetic background caused by local drift and selection. Local variation in genetic background constitutes a selective barrier to spread of the "sometimes advantageous" gene. Negative correlations between effects within and between populations are believed to be responsible for hybrid fitness reduction and so contribute to speciation (Charlesworth et al. 1987; Moreno 1994; Johnson and Wade 1996). Changing the sign of an allelic main effect *requires* epistatic gene action or strong genotype-by-environment interaction (Wade 1992, 1996). In contrast, in the LST genic effects are essentially constant and genes with negative epistatic interactions do not co-occur in any ancestral population. The epistasis responsible for hybrid fitness reduction in the LST is introduced ad hoc to explain hybrid incompatibilities caused by genes fixed de novo in allopatric populations (e.g., Charlesworth et al. 1987; Orr and Orr 1996; Gavrilets 1997). With epistatic genetic variation for fitness existing *within* an ancestral population, reproductive isolation and speciation can develop in the SBT by drift and selection as opposed to LST's de novo adaptive variations introduced by mutation in allopatry. Below, we show how to evaluate the likelihood of this kind of epistasis empirically using quantitative genetic methods to directly connect micro- and macroevolutionary processes.

It is well known that inbreeding and random drift convert dominance variance to additive variance by increasing homozygosity and exposing deleterious recessives to purifying selection (Robertson 1952; Willis and Orr 1993). In a randomly mating population, a locus with allelic dominance but no additive effect ($a = 0$, $d > 0$; see Falconer, 1989, p. 129) contributes $2d^2p_Aq_a(p_A - q_a)^2$ to the additive variance. Two loci with pure additive-by-additive epistasis *each* contribute approximately $2a^2p_Aq_a(p_B - q_b)^2$ to the additive variance, a value comparable to that of a purely dominant locus. (Note the explicit dependence of the additive variance at locus A on its epistatic partner, locus B.) In a metapopulation, at most one-quarter of the original dominance variance within demes is converted to additive variance and this occurs when F_{ST} is in the range of 0.25 to 0.30 (Goodnight, unpubl.). In comparison, one quarter of the original additive-by-additive epistatic variance is converted to additive variance at an F_{ST} of only 0.0625 (see further discussion below). Furthermore, the conversion of epistatic to additive variance affects the potential for local adaptation, whereas the conversion of dominance variance affects primarily purifying selection.

Some of the predictions of these nonadditive models have been tested in the laboratory. In fruit flies (Lopez-Fanjul and Villaverde 1989), house flies (Bryant and Meffert 1988, 1990, 1992, 1995, 1996a,b; Bryant et al. 1990; Meffert and Bryant 1991, 1992; Meffert 1995), and flour beetles (Wade 1985; Pray and Goodnight 1995, 1997; Wade et al. 1996), the additive genetic variation for many traits increases after inbreeding or a population bottleneck. However, these studies have not partitioned the relative contributions of dominance and epistasis to the observed increase (Willis and Orr 1993). Results from interpopulation crosses in the pitcher-plant mosquito (Hard et al. 1992, 1993a,b; Bradshaw and Halzapfel 1996; Armbruster et al. 1997), flour beetles (e.g., Wade 1985; Wade et al. 1994, 1997; Wade and Griesemer 1998), and fruit flies (Blows 1993; Blows and Sokolowski 1995) are also consistent with the novel theoretical predictions of the epistatic models. The large among-sire variance reported in the half-sib hybrid interspecific crosses of Wade et al. (1994, 1997) cannot be due to dominance variance by virtue of the half-sib design (Falconer 1989, p. 166). (Note that Tonsor and Goodnight [1997] found no significant differences in heritability for traits in a small natural population of *Plantago lanceolata* comparing random vs. nearest neighbor matings.) These theoretical and empirical findings regarding the interconversion of variance components change the significance of nonadditive genetic variance for *both* theories. Neither Fisher nor Wright discussed the conversion of epistatic to additive genetic variation within local demes (Goodnight 1987, 1988; Whitlock et al. 1993), its contribution to genetic diversity between demes (Goodnight 1995), or its contribution to reduced hybrid fitness or "outbreeding depression" (Thornhill 1993) between demes.

Three additional theoretical results are important to understanding the role of random genetic drift in crossing an adaptive valley, an important feature of the SBT. First, Whitlock (1995) has shown that random genetic drift not only changes the phenotypic mean but also may increase the genetic and phenotypic *variance* of a population. Points on the mean fitness surface are averages and depend upon the variance (and other shape parameters) as well as the location (i.e., the mean) of the phenotypic distribution. When the phe-

notypic variance increases, fitness valleys between adaptive peaks are diminished and sometimes eliminated. Thus, the fitness landscape is "smoothed" making random genetic drift even more effective "as a trigger" to "change locally the direction of mass selection" (Wright 1978, p. 521, 524). Experimental studies have observed an increased phenotypic variance in several traits after drift (Pray and Goodnight 1995, 1997; see also Bryant and Meffert 1996a,b).

Second, ridges between adaptive peaks on the surface of mean fitness are possible in most complex genetic systems and likely in some (Turelli and Barton 1994; Williams and Sarkar 1994; Gavrilets 1996). The loss in mean fitness for a population traversing such a ridge is less than that incurred by crossing the deeper adaptive valleys. However, the likelihood that a population will move from peak to peak by traversing the ridge instead of the valley is not known. (The ridges associated with "Dobzhansky-type" epistasis are postulated to arise in allopatry by the de novo fixation of alternative alleles. They are ridges only for the reference hybrid population created by interpopulation crosses [Gavrilets 1996]. They are not traversed in the sense of Wright's SBT.)

Third, following Hill and Robertson (1966), Barton (1995) has investigated how finite population size creates interference between simultaneously selected loci, slowing the rate of evolution of each. The interference becomes stronger, the tighter the linkage and the greater the number of simultaneously selected loci (Wright 1978; Barton 1995). Interference will extend the time to complete adaptation because, not only do the alleles with the greatest effect on fitness evolve first and interfere with one another in the process, but weaker, favorable alleles at other loci suffer an increased probability of loss. Put differently, the probability of loss of a favorable allele is greater than the classical value of $(1 - 2s)$ (e.g., Haldane 1927; Li 1997; see also Otto and Whitlock 1997) whenever there are other simultaneously selected loci in the population. Even if an allele is advantageous everywhere, it is unlikely to be the biggest regressor on fitness everywhere.

In toto, the novel empirical and theoretical findings of the past 15 years warrant a reevaluation and refinement of the Wright-Fisher debate. *Both* theories are affected, albeit in different ways, by the phenomena of conversion, interference, and the effects of drift on the shape of the phenotypic distribution. If the additive variance itself derives primarily from gene interactions, it is not clear to us which theory is the more parsimonious. In the sections below, we use the framework laid out in Table 1 to reevaluate the differences between Wright's SBT and Fisher's LST in light of recent theoretical and empirical findings and to suggest areas for further research.

The Central Problem of Evolution Theory

The central problem of evolution for Wright was explaining the origins of adaptive novelty, whereas for Fisher it was explaining the refinement of existing adaptations (Table 1). Using engineering analogies, Wright was interested in a system that permits a species to find a global solution, if it exists, to an environmental problem for which there are many different local solutions of varying quality. Fisher was interested in a system that permits ever-increasing precision of and incremental refinement toward an existing optimal solution. Several of the differences between the SBT and the LST derive from this difference in conception of the central problem.

For Fisher, most (if not all) species consisted of single, very large, and randomly mating (panmictic) populations with a long history of adaptation by natural selection. It is a major problem in the LST to maintain sufficient genetic variation for the selective refinement of existing adaptations in the face of continual deterioration of the environment. Natural selection acting over long periods of time in very large populations to hone adaptations will fix even very weakly favorable genes. The Wright-Fisher controversy over the evolution of dominance centers on this belief of Fisher and Wright's contesting its validity in small populations (cf. Provine 1971; Charlesworth 1979; Kacser and Burns 1981; Orr 1991). Adaptation under the LST is limited by the balance between mutation and natural selection and by the duration of the fitness optimum.

Fisher's fitness optimum is defined as the *average* over all fine-scale temporal and spatial variations in ecology. He is explicit about this when discussing the average effect of a gene on fitness: "the population used to determine its value comprises, not merely the whole of a species in any one generation attaining maturity, but is conceived to contain all the genetic combinations possible, with frequencies appropriate to their actual probabilities of occurrence and survival, whatever these may be, and if the average is based upon the statures attained by these genotypes in all possible environmental circumstances, with frequencies appropriate to the actual probabilities of encountering these circumstances" (Fisher 1958, pp. 30–31). Change in this global average environment is gradual and incremental. It permits Fisherian uphill selection to always proceed with the only essential evolutionary forces being mutation and natural selection.

The contrast between Fisher and Wright in the conception of the environment is stark. In Wright's view, "the environment, living and non-living, of any species is actually in continual change" (Wright 1931, p. 167) and includes biotic and abiotic components as well as the special environment of genotypic background (owing to epistasis). A spatially variable and constantly changing environment creates multiple adaptive peaks on the surface of mean population fitness that change with time "like waves on the ocean surface." The genetic subdivision of a metapopulation *prevents* the global averaging of the environmental variation into a single optimum envisioned by Fisher and compromises the definition of the average effect of a gene on fitness (see below). The central problem for the SBT is to explain the continuous origin of adaptive novelty in response to the milieu of a changing and variable environment.

The genetic system in the SBT has two different functions: a mechanism for preserving adaptive gains and a mechanism(s) for searching for or maintaining responsiveness toward changing fitness optima. The latter function is addressed by mutation in the LST. Fisher's concern with Wright's process is that the SBT trades off precision and selective refinement in favor of random movement away from current adaptation and toward a global optimum that may not exist.

Wright's concern with Fisher's process is that it is unlikely to find a global optimum in a sea of local solutions when adaptive change is dependent upon or constrained by initial conditions and local context. Whereas Wright's process is not as efficient at maintaining and refining existing adaptation, Fisher's process is poorer at moving through a complex fitness space (because it gets stuck at local optima) or at tracking large environmental changes.

Major Processes of Evolutionary Change

In both theories, natural selection is the only evolutionary force necessary for and capable of producing adaptation, the conspicuous fit of organisms to the environments in which they live. They differ, however, in the roles accorded the nonadaptive evolutionary forces like mutation, recombination, random drift, and migration. These forces ultimately permit a population to adapt by generating genetic variation between individuals or groups of individuals. We refer to these as the "dispersion forces" (called the "searching forces" in Toquenaga and Wade 1996) because they result in the genetic dispersion of individuals, groups, or lineages around a fitness optimum.

The primary focus Fisher's LST and much of population genetic theory for the past 40 years has been explaining the origin and maintenance of genetic variability within populations at or near to an adaptive, global optimum. Most models of population and quantitative genetics view the dispersion forces as impediments to adaptation because they move individuals (mutation, segregation, and recombination) or whole populations (random drift and migration) away from the optimum under natural selection. The more stable the environment, the stronger the selection *against* the dispersion forces and the greater the refinement of adaptations. The stronger the emphasis on adaptation, the lesser the role that the dispersion forces play in evolutionary theory. For example, in the evolutionarily stable strategies (ESS) school of evolutionary thought (Maynard Smith 1982), there is a singular focus on optimization. It has eliminated consideration of the dispersion forces altogether as part of its move away from formal genetic models in favor of a nongenetic, game theory approach. If the optima are unchanging or if the rate of adaptation is very fast relative to the rate of change in the optima, this view point can be strongly and cogently defended (e.g., Hammerstein 1996); it is a useful tool in evolutionary investigation. But, if the time scale of environmental change is commensurate with that of adaptation, then the dispersion forces play a greater role in defining the limits to and the possibilities for adaptation. Constraints of genetic architecture and genotype-by-environment interactions make some adaptive optima inaccessible. These constraints on adaptation are omitted by assumption in ESS theory.

In a population at a fitness optimum, selection reduces the rate of the dispersion forces because, on average, they create variation in the direction away from the optimum. A fitness cost or "load" is generated whenever a dispersion force operates. For mutation, the familiar textbook argument (e.g., Hartl and Clark 1989; Bell 1997) is that mutations are likely to decrease fitness because they will be in the direction away from the optimum. Likewise, mutations of small effect are more likely to be advantageous than those of large effect because the larger the deviation away from the optimum, the more likely it is to be deleterious. Fisher (1958) used the analogy of a microscope in which small refinements of focus in the vicinity of the optimum are more likely to result in the clear resolution of an object than are coarser changes in focus (but see Kimura 1983; Orr and Coyne 1992). Similarly, random genetic drift in a population at an adaptive optimum rarely follows the movement of an adaptive peak on the fitness surface. The smaller the size of the deme, the larger the random deviations away from the optimum genetic configuration. Also, it becomes more likely that drift will move a population off an adaptive peak to a lower mean fitness: "Genetic drift causes local populations (demes) to temporarily lose fitness" (Coyne et al. 1997, p. 163). This effect leads to the view that natural selection and random genetic drift are opposing forces, even though the *average* allele frequency change caused by drift is zero. For these reasons, in the vicinity of a fitness optimum, those lineages with lower rates of mutation, random genetic drift, recombination, or migration will tend to have higher mean fitness on average than those with higher rates.

In a changing environment, the adaptive value of mutation and the other dispersion forces is different. Crow (1986, p. 206) expressed it well: "We can reasonably expect that there is an optimum mutation rate. If the rate is too high, too many harmful mutations occur and the species or strain loses fitness and may become extinct in competition with others. On the other hand, if the rate is too low, the genetic variability may not be sufficient to keep up with a changing environment." Thus, the adaptive reduction in the mutation rate is limited ultimately by the stability and duration of the fitness optimum. The longer a population persists at a fitness peak, the greater the adaptive reduction in the rate of mutation. The reduction of a species' mutation rate below some limiting value places it at risk of extinction in the face of environmental change. This, and many arguments favoring adaptability per se (e.g., Levins 1968), explicitly invoke a balance between two levels of selection: individual selection lowering the mutation rate within populations and "group selection" by differential extinction of populations maintaining it above a minimum value.

Similar considerations in regard to recombination led Franklin and Lewontin (1970) to pose the question "Is the gene the unit of selection?" and led Turner (1967) to ask "Why does the genome not congeal?" Equivalently, we could ask why recombination persists in the face of segregation load, the creation of less fit progeny by the genetical dispersion force of recombination (or segregation). "In the long run, the tightest possible linkage will give the highest possible fitness, so we expect, as Fisher suggested, that recombination values will evolve toward zero if there is any genetic variance for recombination" (Lewontin 1974, p. 297). In contrast, an evolutionary advantage for recombination is emphasized most often in discussions of the adaptive advantage of sexual over asexual reproduction in a *changing* environment. Indeed, understanding the evolutionary advantage to sexual reproduction is considered equivalent to finding an adaptive advantage for recombination (e.g., Felsenstein 1974, 1988; Brooks 1988). Theory shows that sexual reproduction

can be favored over asexual reproduction, especially in variable environments. A variety of different kinds of environmental variation have been described in this context, including environments that change unpredictably with time, space, genotypic competitor, or the rapid coevolution of parasites and pathogens (Bell 1997). Crow (1986, p. 210) argued that recombination permits "a Mendelian population to maintain the maximum potential variance with a minimum of standing variance. It can respond to changes in the environment by producing recombinants, some of which may be better adapted to the new environment than any member of the current population."

Like mutation, recombination is advantageous in a changing environment but disadvantageous in a constant one. An "optimal" recombination rate is determined by the stability and duration of fitness peaks. These in turn are determined by the stability and constancy of the environment. Like the arguments for an optimal mutation rate, selection within populations at an optimum favors lower recombination rates. The differential extinction of populations during periods of environmental change favors a higher recombination rate. Selection between groups or lineages is an explicit component of the SBT (phase III), but not of the LST.

The dispersion forces that are impediments to the LST are essential for solving the central problem of evolutionary biology in the SBT. The dispersion forces do not cause adaptation in the SBT, but they do affect the evolutionary trajectory of a population across the adaptive landscape. Indeed, in a stable environment and without random genetic drift there would be no movement at all across the adaptive landscape because a population would evolve toward and be permanently captured by the nearest local peak. Random genetic drift in the SBT serves as a "trigger" affecting the local trajectory of mass selection (Wright 1978, p. 521, 524). Under Wright's scenario, random genetic drift can move the population across an adaptive valley and into the domain of attraction of a different peak, at which time natural selection takes over. It is easier for a population to escape from a low peak by drift than from a high one. Hence, by trial and error and without phase III, a species will work its way to the highest local fitness peak by drift alone but "the rate of progress is extremely slow" (Wright 1982). Increases in the phenotypic variance by drift can facilitate this process by smoothing the fitness landscape (Whitlock 1995). This local movement by drift alone among a cluster of nearby peaks does not result in the ongoing adaptive evolution envisioned by Wright in which the major peaks are far apart. Thus, he proposed another adaptive process, phase III interdemic selection, for these transitions.

When different demes in a metapopulation arrive at different local peaks with different heights on the landscape of mean population fitness, interdemic selection becomes an important directional force for adaptation in the SBT. It occurs by the phase III mechanism of differential migration of individuals out from regions of high fitness and into regions of lower fitness (Wright 1931, 1978; Wade and Goodnight 1991; Wade 1996; Wade and Griesemer 1998). To understand why population subdivision accelerates the spread of an adaptive gene combination, consider the linkage disequilbrium or genetic covariance associated with an adaptive gene complex. The genetic differentiation of demes means that the total linkage disequilibrium, D_T, can be partitioned into within-deme, D_{within}, and among-deme, D_{among}, components (just like partitioning variances). The among-deme component of D is *not* affected by recombination, which occurs only within demes. Thus, population subdivision per se *limits* the power of recombination to break up favorable gene combinations. Furthermore, phase III migration, m_{III}, imports the among-deme, *adaptive* disequilibrium, which is greater than D_{among}, into low fitness demes, where it replaces a portion of the within-deme disequilibrium eroded by recombination. (With random migration, m, mD_{among} [$< m_{III} D_{among}$] is imported into all demes.)

A "peak shift" (Wright 1931, 1969) is the genetic transformation of a low fitness deme after it receives migrants from a deme(s) of higher fitness and natural selection subsequently carries it to the higher fitness peak. In most theory (e.g., Crow et al. 1990; Barton 1992; Moore and Tonsor 1994), there are only two demes and D_{among} is near its maximum by assumption. Random migration alone (m) can initiate a peak shift by carrying a low fitness deme into the domain of attraction of a higher fitness peak because mD_{among} is high. In the SBT, Wright saw that random genetic drift and selection "amplified" the "field of variability" created by mutation (i.e., they create D_{among}) and interdemic selection then "amplified" the force of local, *within-deme*, natural selection (Wright 1982, p. 630) via $m_{III} D_{among}$. In the LST, there is always a conflict between natural selection building up favorable gene combinations and recombination breaking them apart, and the heritability of traits determined by gene combinations is low. In the SBT, this conflict is tipped in favor of selection because the metapopulation genetic structure limits recombination and because natural selection within demes is enhanced by interdemic selection.

Just as adaptation under Fisher's LST is limited by the rate of occurrence of adaptive mutations at single genes, adaptation under Wright's SBT has been characterized as being even more severely limited by the waiting time for double or compensatory mutations (Michalakis and Slatkin 1996; Phillips 1996). However, fixing two advantageous mutations de novo in small populations is also problematic for the LST owing to interference between simultaneously selected loci (Barton 1995). Interference increases the probability of loss by drift of the more weakly favored allele (Barton 1995). Thus, fixing two genes, each on its own merits (i.e., additively), requires on average more than two mutational events in the LST. The greater the interference (e.g., with tight linkage and small population size), the more interference will make the fixations sequential as opposed to simultaneous. In contrast, in the SBT we expect simultaneous as opposed to sequential fixations because selection acts directly on the gene combination. In addition, the field of possible adaptive gene combinations is vaster than the field of possible adaptive additive genes because the number of combinations increases to the power of the number of genes. This is true for both theories, but only the SBT has a mechanism to capitalize on it and incorporate it into the evolutionary process.

The Ecological Context of Evolution

In the LST, the ecological context for evolution is a very large and randomly breeding population where each gene

experiences every possible genetic background exactly in proportion to its occurrence (Fisher 1958, pp. 30–31). Here, epistatic genetic effects are unimportant though, for genomes consisting of more than a few loci, the astronomical number of possible genotypes requires that population size also be astronomically large. None of the effects known to slow the rate of adaptive substitution in finite populations, such as background effects or interference between simultaneously selected loci (Hill and Robertson 1966; Maynard Smith and Haigh 1974; Barton 1995), need be considered. In very large populations, the probability of stochastic loss of favored alleles is diminished, interference between selected loci is negligible (Barton 1995), and background effects are averaged out. If adaptive mutations are sufficiently rare and the conditional time to fixation sufficiently fast, then two favored loci will never be in transit at the same time and interference cannot occur. Thus, the ecological context assumed by the LST dictates the essence of the adaptive process.

Wright imagined that the membership of most species was distributed into small, semi-isolated breeding groups, violating the assumptions of panmixia and large population size. In such metapopulations, the role of local natural selection is somewhat diminished, and random genetic drift and interdemic selection become more important evolutionary forces. Interference between simultaneously selected loci in finite demes increases the probability of stochastic loss, especially for weakly selected loci (Barton 1995), and slows the overall rate of substitution of favorable genes. Natural selection can diminish interference by favoring increased recombination rates. However, the evolution of recombination rates is a third-order process, which is weaker than Fisher's model for the evolution of dominance, and is unlikely to be important in small populations.

In some studies, the dynamics of deme extinction and colonization have been characterized as "source-sink" (Pulliam 1988; Dias 1996). "Sinks" are demes with rates of population increase less than one. They tend to go extinct shortly after being founded (Hanski and Simberloff 1997). Other demes, called "sources," tend to persist for longer periods of time, sending out colonists to vacant habitats. A common interpretation of such a "mainland-island" metapopulation (Harrison 1994; Gomulkiewicz and Holt 1995) is that the transient sinks are ecologically unimportant repositories of the emigratory excess from the mainland sources. As such, they are also evolutionarily unimportant. Whenever there is conflict between a gene's adaptive value in the source population and its value in the sinks, the source population dominates the evolutionary trajectory.

For calculating Wright's F_{ST}, the sinks would appear to be irrelevant and even misleading. Nevertheless, some species of mice (*Mus domesticus* and *M. musculus*) have classic mainland-island metapopulations with large stable populations, often centered around barns or feed mills, and much smaller populations, centered around haystacks or tussocks, that are so prone to extinction that they are difficult to resample (Ardlie 1998; Ardlie and Silver 1998). These transient and apparently peripheral island sinks harbor a unique genetic element, the t-allele complex, that is not found or found at only low frequency in the larger source populations (Ardlie 1998; Ardlie and Silver 1998). This complex has been shown to consist of more than seven interacting genes and the age of the gene complex is estimated to be significantly older than the species in which it has been described (Delarbre et al. 1988; Lyttle 1991; Wu and Hammer 1991; Silver 1993; Ardlie and Silver 1996). This is evidence that the common interpretation that the transient islands are ecologically and evolutionarily unimportant must be incorrect. Far from being evolutionary dead ends, these peripheral island sinks have served as a long-term refuge for the build up of a multigene complex that otherwise would have been lost.

The Genetic Basis of Evolutionary Change

For Wright, the relationship between genotype and phenotype is complex, involving both universal pleiotropy (several traits affected by the same allele) and universal epistasis (interactions between alleles at different loci). Thus, "evolution depends on the fitting together of favorable complexes from genes that cannot be described in themselves as either favorable or unfavorable" (Wright 1969, p. 105) and context or genetic background is the essence of evolution (see also Lewontin 1974, p. 318). Population subdivision amplifies the rate of adaptation. Fisher acknowledged gene interactions, but considered them unimportant and akin to nonheritable environmental variation. In the LST, the evolutionary fate of a gene is determined solely by its average effect on fitness, defined as the "regression in the actual population of the genotypic measurement [fitness] on the number of G genes" (Fisher 1941, p. 54). Fisher's statistical abstraction of a gene's average effect on fitness has become reified as a fixed property of a gene *independent of background* in the building-block models of evolutionary genetic theories. The practice of estimating narrow-sense heritabilities from full- and half-sib breeding designs reinforces the common notion that genes have independent, additive effects. Similarly, the empirical study of single gene, visible mutations of large phenotypic effect and null alleles reinforces this view of the constancy of gene effects independent of background. In contrast, Wright holds that, evolutionarily speaking, one gene is no gene: genomic background determines the evolutionary trajectory of a gene.

In the very large populations of Fisher's theory, considerations of the genetic architecture are not relevant and the additive effect of a gene changes for only two reasons: as a function of the mean of its population and as a function of its own frequency within the populations. Little of consequence is lost by lumping epistatic gene interactions with the nonheritable environmental variance. This is not a statement about the existence of epistasis, but rather one about its lack of importance and irrelevance to the evolutionary process. When genes are present in all possible combinations in proportion to their frequency (Fisher 1958, pp. 30–31), the statistical description of the average additive effect does capture the essence of a gene's contribution to adaptive evolution, at least for one generation, and for subsequent generations if linkage disequilibrium between simultaneously selected loci is ignored.

Few, if any species, exist as single panmictic populations (Hastings and Harrison 1994). Genetically subdivided population structures are the norm. Average values of F_{ST} for

single loci are very commonly found to be in the range of 0.03–0.15 for insects (McCauley and Eanes 1987; McCauley et al. 1988; McPheron et al. 1988; McCauley 1989, 1993; Rank 1992; Whitlock 1992), including *Drosophila melanogaster* (Singh and Rhomberg 1987). Values for plants with mating systems that include selfing and local inbreeding can be much higher (0.25–0.70); (Hamrick et al. 1979; Hamrick 1983; Loveless and Hamrick 1984; Govindaraju 1988). To what degree do these levels of metapopulation genetic structure affect the genetic conception underlying Fisher's LST? Does this level of genetic substructuring have the biological significance accorded to it by Wright's SBT? We show below that, for observed F_{ST} values, epistasis cannot be ignored and, in fact, it limits the adaptive process as conceived by Fisher.

Breeding Value in Metapopulations.—First, consider the concept of the breeding value of an individual in a single large, panmictic population, where each sire is mated to multiple dams to produce multiple offspring. We represent the phenotype of the lth offspring (l = 1, 2, . . . L) of the kth dam (k = 1, 2, . . . K) and jth sire (j = 1, 2, . . . J) as Z_{jkl}. Fisher (1941) defined the breeding value of a sire as the average deviation from the population mean of the offspring produced by randomly mating that sire to all females in the population. Thus, if we set the population mean at zero, the breeding value of the jth sire is given by

$$A_j = (\Sigma\Sigma Z_{jkl})KL = Z_j. \quad (1)$$

Recognizing that the mean A. equals zero because breeding values are measured as deviations from the population mean, Fisher defined the variance in the breeding values to be V_a, the additive genetic variance,

$$V_a = (\Sigma A_j^2)/J. \quad (2)$$

In a metapopulation with limited gene flow among demes, another level of summation must be added to this expression to recognize the population genetic structure. Consider a sire mated at random throughout the metapopulation as opposed to throughout a single population as above. The phenotype of the lth offspring of the jth sire by the kth dam in the ith deme (i = 1, 2, . . . I) is Z_{ijkl}. Mating each sire to several dams in each of many demes, we can pool the dams based on their deme of origin to obtain

$$A_{ij} = (\Sigma\Sigma Z_{ijkl})/KL = Z_{ij**} \quad (3)$$

We define A_{ij} as the local breeding value of the jth sire in the ith deme (Goodnight 1995). It is the average value of the deviations from the metapopulation mean of offspring produced by the jth sire when mated randomly to dams in the ith deme. (Note that local breeding value is defined as a deviation from the overall metapopulation mean, not as a deviation from the local deme mean. The deviation from the local mean is relevant for describing local adaptation, but here we are discussing Fisher's concept in a metapopulation.)

The variance in breeding values across the metapopulation no longer equals the additive genetic variance (Falconer 1989). The variance among local breeding values, V_{LBV}, becomes

$$V_{LBV} = [\Sigma\Sigma(A_{ij})^2]/IJ. \quad (4)$$

We further partition A_{ij} into separate deme and sire effects as well as the interaction between them:

$$A_{ij} = A_{i*} + A_{*j} + A_{i*j}, \quad (5)$$

where $A_{i\cdot}$ equals $(\Sigma A_{ij})/J$, A_{*j} equals $(\Sigma A_{ij})/I$, and A_{i*j} is $(A_{ij} - A_{i*} - A_{*j})$.

Substituting into equation (4), and recognizing that the partitioning of A_{ij} is orthogonal (i.e., the covariances are zero), yields

$$V_{LBV} = [\Sigma(A_{*j})^2]/J + [\Sigma(A_{i*})^2]/I + [\Sigma\Sigma(A_{i*j})^2]/IJ. \quad (6)$$

Clearly, the variance in local breeding values consists of three separate components: (1) the average variance among-sires within localities, $V_{sires} = (\Sigma[A_{*j}]^2)/J$; (2) the among-demes variance in local breeding value, $V_{demes} = (\Sigma[A_{i*}]^2)/I$; and (3) the average variance due to the interaction between sires and demes, $V_{sire*deme} = (\Sigma\Sigma[A_{i*j}]^2)/IJ$ (see also Goodnight 1995.) Each of these components of the variance in breeding value has a different evolutionary implication. The first component, V_{sires}, determines the *average* rate of adaptation to local conditions within all demes across all sires. It is equivalent to the additive genetic variance only if the metapopulation is a single, infinitely large, panmictic breeding group as assumed in the LST. The assumption that the F_{ST} values observed in nature (for what are assumed to be neutral loci) represent biologically insignificant genetic structure is equivalent to assuming that the last two variance terms in equation (6) are negligible and that the ecological context for Fisher's LST holds exactly.

The second component of variance in local breeding value, V_{demes}, is that owing to genetic differences among demes. In the absence of gene interactions, this is equal to the genetic variance among the deme means and, relative to the sum of components (1) and (2), it should be proportional to F_{ST}, that is, the F_{ST} for breeding value. When migration diminishes genetic differences among demes to a negligible level, then this term is essentially zero for that reason. However, several studies using experimental metapopulations with flour beetles have shown that large, heritable differences in mean deme fitness arise quickly for levels of F_{ST} comparable to those observed in natural populations and do so despite migration rates of 0.05–0.12 (Wade 1979, 1980b, 1982, 1984, 1985, 1988, 1990; McCauley and Wade 1980, 1981; Wade and McCauley 1980, 1984; Wade and Goodnight 1991; Wade and Griesemer 1998). Furthermore, many of these studies have used artificial interdemic selection to show that the observed among-deme variation is heritable and available for a response to interdemic selection. Thus, the empirical data refute the idea that V_{demes} can be ignored in evolutionary discussion.

$V_{sire*deme}$ is the variance component due to interactions between the sire and the demic genetic backgrounds that results from both changes in scale effects and order of effects (like "crossing-style" genotype-by-environment interaction [e.g., Wade 1990]). Among other things, it measures the evolutionary capacity for genetic divergence among demes in response to a uniform selective pressure. In the LST, uniformly good genes with uniform selection do not produce genetic diversity. The greater the ratio of this interaction variance to additive variance, the lower will be the correlation in breeding values between demes. Put differently, when

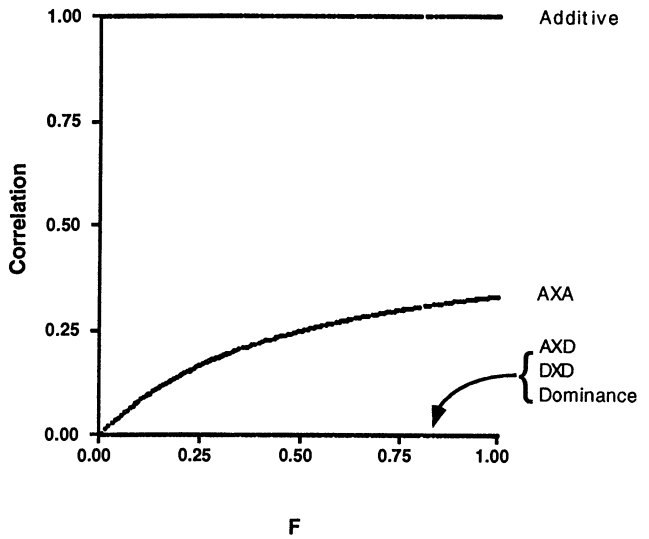

FIG. 1. The correlation between local breeding values as function of the inbreeding coefficient, F, for a model with only additive genetic variance (additive), additive by additive epistasis (A × A), and dominance, additive by dominance (A × D), and dominance by dominance (D × D) variance. (Note that all interactions involving dominance have a correlation of zero.)

$V_{sire*deme} > 0$, alleles favored by selection in one deme can be opposed by an *identical* selection pressure in another deme. Directional selection, which is a cohesive force in an additive world, can become inherently diversifying whenever there is gene interaction (i.e., whenever $V_{sire*deme} > 0$).

To see the evolutionary significance of $V_{sire*deme}$, consider a pair of sires, A and B (Fig. 1). First, assume only additive effects (no dominance or epistasis), so that $V_{sire*deme}$ is zero. If, in a particular deme, the local breeding value of sire A is larger than that of B by some value, D, then this difference will be maintained no matter which deme is used as a source of dams to measure breeding value. In the absence of gene interaction, the genetic covariance across demes of breeding values is very high, essentially one. If V_{demes} is greater than zero, then, although the local breeding values of the two sires will vary from deme to deme, the *difference* between them, D, will remain constant. As long as the direction of selection is the same in all demes, the fitness difference between these two sires will also remain the same. In contrast, compare this with the case of gene interaction, that is, $V_{sire*deme} > 0$ (Fig. 1). The difference between the local breeding values of the two sires, D, is no longer a constant when measured from deme to deme, and may even change sign. Even if the direction of selection is the same in all demes, the fitness difference between these two sires will not be constant from deme to deme. Hence, uniform selection can be genetically diversifying, leading to different outcomes in different demes. Just as genotype-by-environment interactions can result in a change in the order of genotypes from deme to deme (e.g., Via and Lande 1985, 1987; Wade 1990) owing to differences in the environment, a shift in the order of breeding values from deme to deme owing to epistasis ($V_{sire*deme} > 0$) will be genetically diversifying. In this sense, gene-gene interactions and genotype-by-environment interactions are both evolutionarily diversifying. This is one of the most important components of genetic variance in regard to speciation (Moreno 1994; Johnson and Wade 1996).

There is only one experimental study to date that has measured the breeding values of sires across *randomly* differentiated demes in a metapopulation (Wade 1985), although general and special combining ability have been estimated for many artificial strains. In Wade (1985), full- and half-sib progeny from a set of randomly chosen sires were placed singly into each of 10 demes derived from the same stock. The relative fitness of each offspring, that is, the breeding value of fitness, was measured for each sire in each deme. The analysis of variance in relative fitness revealed significant sire and deme effects with a demic effect 18 times greater than the sire effect, although the among-deme F_{ST} was only 0.20. In a strictly additive model, the maximum among-deme component occurs when F_{ST} is 1.0 and then it is only expected to be eight times the V_{sires} in the base population. The large value of V_{deme} is consistent with several other experimental studies of metapopulations with F_{ST} values in the range of 0.03–0.40 (cf. Wade 1996).

A critical question is the value of $V_{sire*demes}$ relative to V_{deme} because, when it is large, there can be a shift in the order of local breeding values from deme to deme. This is perhaps best measured using the correlation among local breeding values,

$$V_{deme}/(V_{deme} + V_{sire*demes}), \quad (7)$$

derived by Goodnight (1995). This can be estimated from the ratio of the variance in the mean local breeding value among sires to the mean variance in local breeding value, namely, V(mean local breeding value)/V(within sires local breeding value). Goodnight (unpubl.) used different levels of inbreeding (F) to simulate population genetic structure and calculated theoretical values for this correlation for local average effects for the standard forms of genetic effects: additive, dominance, additive by additive, additive by dominance, et cetera. We have recalculated this correlation for breeding values. (Average effects are the building blocks of local breeding values. The breeding value of a sire is the sum of the average effects corrected for the population mean. Average effects exhibit the properties we are trying to illustrate.) With only additive genetic effects (see Fig. 2 and eq. [7]), the correlation is one for all values of the inbreeding coefficient, F. This is owing to the fact that, with a completely additive genetic architecture, V_{sires} and V_{demes} can be nonzero (depending on F), but $V_{sires*deme}$ will always be zero (cf. eq. [7] above). In contrast, whenever there is epistasis, for all values of F, the correlation is less than one because $Var(A_{i*j})$ and, consequently, $V_{sires*deme}$, are greater than zero. In particular, the correlation is zero for all gene interactions involving dominance for all values of F.

In Wade (1985), although the $V_{sires*deme}$ component was not significantly different from zero, the *average* correlation of breeding values across pairs of demes was only 0.24 (35 of 45 pairwise correlations > 0), significantly less than one. Hence, knowledge of a sire's breeding value for relative fitness in one deme is not a very good predictor of its value in another deme even in the same metapopulation with an estimated F_{ST} of 0.20. This does not prove that the effect of selection on a given allele would differ among demes, but it

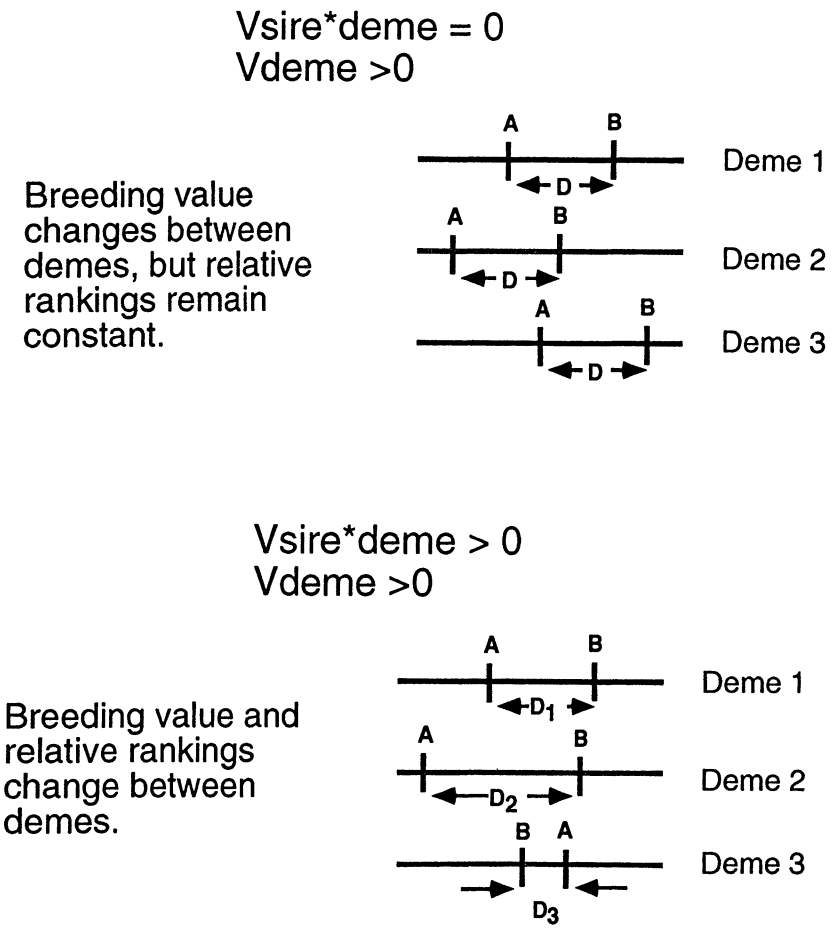

FIG. 2. The effect of $V_{sire*deme}$ on the relative ranking of the breeding values of sires. When $V_{sire*deme}$ is greater than zero, the breeding value of sire B relative to sire A will change magnitude between demes 1 and 2 and will change order between demes 2 and 3. Just as genotype-by-environment interaction of the "crossing-type" changes the favored genotype in different environments, epistasis will have this same effect *in a constant environment* when $V_{sire*deme}$ is greater than zero.

does indicate that, although V_{deme} was large and significant, the correlation across demes is much smaller than the additive expectation of 1.0.

Population Subdivison and Epistasis.—It is important to evaluate more quantitatively the theory presented above in relation to the levels of genetic subdivision observed in natural populations of insects, amphibians, and plants. A relatively simple and familiar formula describes how the additive genetic variance, $V_a(t)$, is diminished within a population by random genetic drift,

$$V_a(t + 1) = (1 - F_{ST})V_a(t). \quad (8)$$

The equilibrium value of V_a is governed by the balance between selection and mutation. This familiar finding changes profoundly in several ways when epistasis is present.

First, whenever the additive-by-additive genetic variance, V_{aa}, exceeds one-third of the additive genetic variance, V_a, in the outbred reference population *any* nonzero value of F_{ST} increases the average V_a within demes instead of decreasing it (Goodnight 1988). Unfortunately, the relative magnitudes of these components of variance, and, in particular, empirical evidence supporting the quantitative threshold, $V_{aa} > (1/3)V_a$, at which conversion replaces the loss of additive genetic variance by inbreeding, is not presently available. Furthermore, for a population with a long history of small size, V_{aa} may be nearly absent within the population but still be contributing to V_a and to $V_{sire*deme}$ (e.g., Tonsor and Goodnight 1997).

Nevertheless, the empirical evidence for the existence of epistatic genetic variance is incontrovertible. It has been shown in studies of recombination load (e.g., Speiss 1958; Dobzhansky et al. 1959), outbreeding depression (Burton 1990; Lynch 1991; Ellstrand 1992; Hard et al. 1992, 1993a,b; Waser and Price 1994; Linhart and Grant 1996; Rhymer and Simberloff 1996; Smith and Skulason 1996), F_2 breakdown (reviewed in Wright 1978 and Geiger 1988; Burton 1990; Blows 1993; Blows and Sokolowski 1995; Breewuer and Werren 1995), and almost all experimental studies involving interspecific crosses, especially those concerning fluctuating asymmetry in hybrids (Markow and Ricker 1991; Wade et al. 1997) and the genetic basis of Haldane's rule (cf. Cabot et al. 1994; Wu and Palopoli 1994; Hollocher and Wu 1996; Wu et al. 1996). The recent molecular genetic studies of the three-dimensional structure of many water-soluble proteins indicate clearly that protein function is not linearly mapped along a DNA sequence (Hunter 1996). Recent reviews by

Whitlock et al. (1996) and Fenster et al. (1997) have summarized the evidence for the ubiquity of epistatic variance and placed it in an evolutionary context (see also Moreno 1994).

The second general theoretical finding (Whitlock et al. 1994) is one that can be applied to the values of F_{ST} observed in natural populations. The *average* fraction of the additive-by-additive epistatic genetic variance, V_{aa}, that is converted to additive genetic variance, V_a, within local demes is approximately equal to $4F_{ST}(1 - F_{ST})$ when F_{ST} is small. Thus, for the range of F_{ST} values characterizing natural populations of insects (McCauley and Eanes 1987; McCauley et al. 1988; McPheron et al. 1988; McCauley 1989, 1993; Rank 1992; Whitlock 1992), 12% to 60% of the nonadditive genetic variance is made available for local adaptation within demes by drift. For plants (Hamrick et al. 1979; Hamrick 1983; Loveless and Hamrick 1984; Govindaraju 1988) and salamanders (Routman et al. 1994; Highton 1995), with higher average values of F_{ST} the figure is higher still: 75% to 85% of the epistatic genetic variance is made available for local adaptation by conversion. Thus, random genetic drift and epistasis are potentially sources of additive genetic variance for fueling adaptation to local conditions within natural metapopulations. They may create more variance on a per-generation basis than mutation (Wade 1996).

A third general theoretical prediction (Whitlock 1995) is that, whenever there are X-X and X-autosome gene interactions, then the homogametic sex will have more additive genetic variance than the heterogametic sex. This is the opposite of the prediction for X-linked genes with either additive or dominance variance (Charlesworth et al. 1987; Whitlock and Wade 1995), in which case the homogametic sex should have a lower additive variance. In the study of relative fitness in the experimental metapopulation (Wade 1985), there was a significant sex difference in the among-sire component of genetic variance. The estimate for the homogametic females was positive ($P < 0.0007$), whereas that from their heterogametic brothers was negative and nonsignificant.

For the same reasons, we expect to find a greater additive genetic variance in the homogametic than in the heterogametic sex in the genetics of interspecific hybrids. One empirical generalization is Haldane's rule (Haldane 1922). It states that, in interspecific crosses, the heterogametic sex will be rare, absent, or sterile more often than the homogametic sex (Coyne 1992; Wu et al. 1996) because deleterious epistatic interactions between genes from the two hybridized species are exposed in the heterogametic sex more frequently than in the homogametic sex. Significant genetic variance for traits of interspecific hybrids expressing Haldane's rule has been found segregating within *T. castaneum* (Wade and Johnson 1994; Wade et al. 1994, 1997). In both full- and half-sib hybrid crosses, the variance among sires is greater for the numbers of homogametic female hybrids than for the numbers of heterogametic male hybrids (Wade, unpubl. data). These data indicate that the variation observed from sire to sire in the frequency of hybrid males, that is, in Haldane's rule, is owing more to among-sire variations in the numbers of hybrid daughters than it is owing to variations in the numbers of hybrid sons. The dominance hypothesis put forward to explain Haldane's rule (Muller 1942; Turelli and Orr 1995) predicts that, if the frequency of hybrid males varies from half-sib family to half-sib family, it will do so because of genetic differences between sires affecting the viability of their hybrid, heterogametic sons. The empirical observation in flour beetles is the opposite: the frequency of hybrid males varies from half-sib family to half-sib family because of genetic differences between sires in the numbers of their hybrid daughters. However, these observations are consistent with the sex difference predicted by the X-X and X-autosome epistatic model of conversion (Whitlock 1995). Genes currently segregating within *T. castaneum* interact with at least some of the genes that became fixed in *T. freemani* as the two species diverged from a common ancestor. The ancestral epistatic interactions are expressed in the full- and half-sib hybrid crosses as among-sire variation, an extreme, but biologically important, example of conversion.

The Process of Speciation

The two major features of the biological world that Darwin attempted to explain are (1) adaptation or the amazing fit of organisms to the environments they inhabit, and (2) biological diversity, the very large number of different species. Although Darwin's theory of evolution by natural selection successfully explained the first pattern, his principle of diversification through character displacement and species extinction has not been as successful explaining "how the lesser difference between varieties becomes augmented into the greater difference between species" (Darwin 1859, p. 111). Coyne (1992) reviewed the empirical data on the genetic basis of reproductive isolation and concluded that Darwin's "mystery of mysteries" still had no general explanation.

In a purely additive genetic world, there can be no speciation owing to an intrinsic genetic mechanism, such as incompatible gene combinations. Speciation in Fisher's LST can occur owing to divergent selection in isolated populations where interpopulation hybrids have lowered mean fitness because they are not as fit as the pure parental types in either habitat. This kind of outbreeding depression depends upon the ecological relationship between the interpopulation hybrids of intermediate phenotype and the environments favoring the adaptive divergence of the parental types. Hybrids are not of low fitness for an intrinsic genetic reason independent of the environment. In intermediate environments, hybrids might be fitter than either parental type.

In the LST, the concept of *intrinsic* genetic incompatibility after a period of selective divergence owing to incompatible epistatic combinations is entirely ad hoc (Charlesworth et al. 1987) because epistasis is not considered a relevant component of the genetics of within population adaptation. In the traditional model, incompatible gene combinations do not exist within the ancestral population nor do they exist *within* any of the descendant populations. By definition, they are selected against and cannot be maintained as stable polymorphisms within a population (Charlesworth et al. 1987; Orr and Orr 1996). Thus, in the LST, the entire process of genetic differentiation between the populations destined to become new sibling-species occurs during the period of allopatry (Orr and Orr 1996). Mutation introduces new, neutral

or adaptive variants into each isolate where they become fixed by random genetic drift or natural selection. Coincidentally, the substitutions in one population are incompatible in another allopatric background(s) that itself has been changing simultaneously by mutation, drift, and positive selection. In the LST, speciation will be slower than in the SBT for two reasons. First, the waiting time for the occurrence of multiple and adaptive mutations in two (or more) allopatric populations is long. Adaptive mutations arise much more rarely than neutral or deleterious mutations (see above). Secondly, after the mutations arise, there is the additional time necessary for fixation of the mutations by random drift or natural selection (Charlesworth et al. 1987; Orr and Orr 1996), the conditional time to fixation (Li 1997). The rate of origination of interpopulation genic incompatibility, which confers the intrinsic postmating reproductive isolation, is unknown because epistasis is not an explicit feature of the models until divergence is complete. When incompatible gene combinations are defined retrospectively (e.g., Orr and Orr 1996), no constraints are placed on the order of gene substitutions within demes. When genetic incompatibilities are defined prospectively, populations are restricted from passing through incompatible genotypic states.

In contrast, gene interactions are an essential feature of local adaptation in Wright's SBT: "The effects of multiple loci on a character in general involve much nonadditive interaction (universality of interaction effects)" (Wright 1969, p. 60). The importance of epistasis is especially true for fitness itself: "Interaction effects . . . must, however, almost be the rule in the character that is of first importance in population genetics. This is selective value." (Wright 1969, p. 104). Given epistasis for fitness, there are important implications for speciation of the local conversion of nonadditive to additive genetic variance by random genetic drift and natural selection.

Consider, as in the example above, two allopatric populations derived from the same ancestral population, but with epistatic effects represented by a random distribution centered at zero. In the first generation after separation from a common ancestor, it is clear that interpopulation hybrids are no different in fitness than intrapopulation crosses. Because the additive and additive-by-additive components of genetic variation are defined orthogonally, intrapopulation genetic change does not and cannot change the *average* effect of epistasis on fitness of the interpopulation crosses. Whatever the local selective regimes, uniform or diversifying, and no matter how the random paths of drift wander, the *average* effect of epistasis on the interpopulation hybrids remains zero because the distribution of the effects is defined as random and centered about zero. However, the epistatic variance, V_{aa}, within both populations is converted to additive genetic variance, V_a, and contributes to the response to selection in each. Within both descendant populations, natural selection enriches those gene interactions that are positive for fitness (see also Wade 1992, 1996). However because many of the gene frequency changes are random in the two descendant populations, the genetic architecture underlying V_a is different and population specific, with the among-deme differences increasing with time. As a result, the average epistatic interaction within populations becomes positive whereas the average interpopulation interaction for fitness remains at zero. Hence, the average *ratio* of fitness in an allopatric cross relative to that of a sympatric cross will be less than one, which is the characteristic signature of outbreeding depression and postzygotic isolation. With ubiquitous epistatic interactions for fitness and with the genetic differentiation of local demes within metapopulations, speciation can be a more rapid event under the SBT than under the LST. Indeed, speciation will be the inevitable result of divergence with complex genetic architectures.

Importantly, the ratio of inter- to mean intrapopulation fitness will decrease with time as two populations differentiate by random genetic drift and local natural selection. Both theories predict lowered mean fitness with increasing local adaptation in allopatry. In the LST, this occurs because of the relationship between phenotype and environment; interpopulation hybrids are of intermediate phenotype and are not as fit as the pure parental types in either habitat. In the SBT, the greater the degree of local adaptation, the lower the mean fitness of interpopulation hybrids irrespective of environment because of the epistatic nature of the genetic architecture. It is commonplace to cite the lowered fitness of interspecific hybrids as evidence of epistasis; genes which function well within species cause hybrid inviability or sterility (e.g., Coyne 1992; Charlesworth et al. 1987; Wu and Palopoli 1994; Hollocher and Wu 1996). There is abundant evidence for epistasis underlying hybrid male sterility and inviability in fruit flies, *Drosophila* spp., from fine-scale, molecular genetic studies (cf. review Wu and Palopoli 1994). Nevertheless, the connection between microevolution under Fisher's LST and speciation will remain indirect, ad hoc, and qualitative until formal epistatic models are developed.

The direct, quantitative connection between Wright's SBT and speciation depends upon $V_{sires*demes}$ for fitness that causes directional selection to be inherently diversifying (see above). This direct link in theory between selection and speciation, connecting micro- and macroevolution (anagenesis and cladogenesis), however, remains untested. Until more estimates of $V_{sires*demes}$ become available from laboratory and natural populations, we will not be able to correlate the magnitude of this variance component with the degree of metapopulation genetic subdivision. This relationship will be critical to understanding how rapidly speciation can occur in a given taxon as a result of drift and selection.

Conclusions

In summary, the Wright-Fisher controversy involves the fundamental nature of evolutionary change (the origin of novelty vs. the refinement of existing adaptation), its genetic basis (universal epistasis and pleiotropy vs. additive genetic effects), the ecological context in which it takes place (small, subdivided populations vs. large, panmictic populations), and the mechanisms by which it operates (local, mass selection, random genetic drift, and interdemic selection vs. mutation and mass selection). The biology of the natural world can present difficulties for one or the other theory and may limit the areas and questions to which each theory can be applied (Table 2). For example, with local density regulation or soft selection, Wright's process may be limited, but the *scale* of

TABLE 2. Problems for Wright's shifting balance theory and Fisher's large population size theory.

Natural Phenomenon	Problem
Shifting Balance Theory	
1. Genotype-by-environment interactions	Calls into question the existence of globally adaptive gene combinations
2. Population regulation	Limits interdemic selection by reducing populational heritability
3. Recombination	Lowers heritability of gene combinations and diminishes response to selection
4. Migration among demes	Limits degree of genetic divergence between demes
Large Population Size Theory	
1. Genetic subdivision of populations	Natural selection in local demes is limited by random genetic drift
2. Linkage	Interference between simultaneously selected loci increases the time necessary for adaptive fixation
3. Epistasis	Genetic effects are not properties of genes and depend upon genetic backgrounds
4. Speciation	No epistasis in main body of theory, so there is no direct connection between diversifying selection and genetic mechanisms of speciation

local density regulation is critical (cf. Kelly 1994). Kelly (1996, 1997) found that, despite evidence of local density regulation by competition between neighbors, strong between-patch selection occurred in natural populations of *Impatiens capensis*. Indeed, in the willow leaf beetle, *Plagiodera versicolora*, a phenotypic mechanism for local density regulation, cannibalism within kin groups, was itself the target of intergroup selection in natural populations (Breden and Wade 1989; Wade 1994). Similarly, for Fisher's theory, speciation is particularly problematic because the genetic mechanisms for reproductive isolation involve the indirect response to local adaptation. This is most unfortunate for those who would use Fisher's theory to explain all of adaptive evolution (Coyne et al. 1997), because there is immense interest in speciation genetics and abundant data attesting to the role of gene interaction in reproductive isolation (reviewed in Wu and Palopoli 1994), but no consideration of epistasis in the LST. Goodnight (1995) and Johnson and Wade (1996) have attempted to address this omission.

In the sections above, we considered the degree to which natural populations deviate from the Fisherian ideal and the evolutionary consequences for single- and multiple-gene evolution of such deviations. The "intense controversy" (Provine 1986, p. 232) between Fisher and Wright over gene interactions and effective population size is really an attempt by Fisher to protect the domain of his LST and an attempt by Wright to establish the domain of his SBT. When the special conditions postulated by Fisher of very large and randomly breeding populations with fine-grained environments are obtained, the LST provides an excellent description of evolution. The controversy concerns the degree to which the real world deviates from this Fisherian ideal and validity of the additive genetic approximation when the ideal is not met. Limiting the domain of the LST is not equivalent to establishing the validity of Wright's SBT; several lines of investigation, both theoretical and empirical, tend to support the SBT. In metapopulations with epistatic gene action, the average additive effect is no longer a unitary and invariant property of a gene and it fails as a general descriptor of a gene's contribution to adaptive evolution. When the average effect of a gene changes from deme to deme, selection may favor it in one deme but remove it in another, even when the selection is in the same direction in both demes with respect to the phenotype. Thus, directional selection, which is a unifying force maintaining phenotypic integrity in Fisherian populations, interacts with random genetic drift to become a diversifying force in a Wrightian metapopulation. Wright's genetic theory adds to Darwinian evolution a cogent explanation for the relentless pressure toward speciation and enhanced biodiversity that is lacking in the LST.

Population genetic structure of metapopulations facilitates the evolution of gene combinations in three ways: (1) it permits random genetic drift to augment mutation in exploring the extremely large number of possible gene combinations; (2) it limits the rate of recombination because among-deme differences in gene combination are not recombined; and (3) differential migration imports among-deme linkage disequilibrium into within-deme disequilibrium.

Because selection at one locus increases the variance in offspring numbers, it is experienced as a reduction in effective population size by all other loci. Selection on particular genes within demes thus tends to limit response to future individual selection on other genes, a fact long known to animal breeders. In contrast, phase III interdemic selection, by definition, increases the variance in migration rate reducing the effective migration rate experienced by unselected loci. As a result, random genetic drift increases the among-deme genetic variance for other, unselected loci. If the environment changes to favor another gene or gene combination, the among-deme genetic variation necessary for future interdemic selection is present.

It is common practice to reify additive effects and treat them as properties of genes, independent of genetic and ecological context. Perhaps the fault lies not so much with Fisher's LST as with the uncritical application of it to evolutionary problems it was not meant to solve, such as speciation, or to ecological and genetic contexts in which it does not hold, such as evolution in metapopulations. For the reasons discussed above, accepting the LST over the SBT on the grounds of parsimony (Coyne et al. 1997) does not seem warranted to us.

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