COMMENTS

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IS WRIGHT'S SHIFTING BALANCE PROCESS IMPORTANT IN EVOLUTION?

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In 1997, we published a Perspective (Coyne et al. 1997) that questioned the validity and importance of Sewall Wright's shifting balance theory of evolution (SBT). Our review of both theory and data led us to reject the idea that Wright's shifting balance process has played a major role in adaptive evolution. We supported instead the view of Darwin (as quantified by Fisher) that the main engine of adaptation is natural selection acting on differences among individuals—without genetic drift, population subdivision, and differential migration playing the vital roles hypothesized by the SBT.

Peck et al. (1998) and Wade and Goodnight (1998) each claim that our dismissal of the SBT is premature. Peck et al. (1998) offer a theoretical defense of Wright, claiming that phase III (the movement of populations to higher adaptive peaks) may act more frequently than we proposed. Wade and Goodnight, on the other hand, defend the SBT by discussing experimental studies of group selection and aspects of population subdivision and epistasis. Here we respond to both papers, and conclude that neither offers substantial support for the SBT.

RESPONSE TO WADE AND GOODNIGHT

Wade and Goodnight's (1998) Perspective is useful in helping draw a clearer distinction between the arguments for and against the SBT, and in highlighting issues—such as epistasis, group selection, and population structure—that have sometimes been neglected in evolutionary theory. We hope that our exchange will focus attention on ways to resolve the controversy about Wright's theory. Nevertheless, we still feel that the SBT as a whole has contributed little to our understanding of evolution in nature. The abstract of Coyne et al. (1997, p. 643) states our position:

> We conclude that while phases I and II of Wright's theory (the movement of populations from one ''adaptive peak'' to another via drift and selection) can occur under some conditions, genetic drift is often unnecessary for movement between peaks. The ''third phase'' of the shifting balance, in which adaptations spread from particular populations to the entire species, faces two major theoretical obstacles: (1) unlike adaptations favored by simple directional selection, adaptations whose fixation requires some genetic drift are often prevented from spreading by barriers to gene flow; and (2) it is difficult to assemble complex adaptations whose constituent parts arise via peak shifts in different demes. Our review of the data from nature shows that although there is some evidence for individual phases of the shifting balance process, there are few empirical observations explained better by Wright's three-phase mechanism than by simple mass selection. Similarly, artificial-selection experiments fail to show that selection in subdivided populations produces greater selection response than does mass selection in large populations. The complexity of the shifting balance process and the difficulty of establishing that adaptive valleys have been crossed by genetic drift make it impossible to test Wright's claim that adaptations commonly originate by this process. In view of these problems, it seems unreasonable to consider the shifting balance process as an important explanation for the evolution of adaptations.

In short, we believe that most adaptations in nature can be explained by natural selection acting on intrapopulation variation. We do not, of course, deny the existence of genetic drift, epistasis, pleiotropy, population subdivision, differential extinction and proliferation of groups, or temporally and spatially varying fitnesses (and allelic effects). We claim only that there is little support for the particular mixture of drift, selection, population subdivision, and differential migration invoked by the SBT.

Wade and Goodnight (1998) have not responded to our specific objections to the SBT. As they note (p. 1537), ''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).'' However, their perspective is not ''synthetic'' in the sense of supporting the operation of the SBT as a whole. Rather, they defend the theory by making separate arguments for each of its components, implicitly assuming that if each component can be seen, the theory as a whole must work in nature. As we note below, we find this ''piecemeal'' defense unconvincing.

Wright versus Fisher?

Instead of presenting evidence to refute our arguments against the SBT, Wade and Goodnight (1998) describe a position that they claim we support and then show that this position is unreasonable. They assert, in particular, that we adhere to what they call ''Fisher's 'large population size theory' (LST),'' which maintains that natural populations are not subdivided, allelic effects are independent of environmental and genetic backgrounds, and that speciation occurs through adaptations to divergent ecological circumstance, without evolutionary change producing deleterious gene interactions in hybrids. However, the LST is not ours—or even Fisher's. As far as we know, it has never been espoused by anyone. Nonetheless, Wade and Goodnight portray us as its strong supporters. For example, they note (p. 1549): ''This is most unfortunate for those who would use Fisher's theory to explain all of adaptive evolution (Coyne et al. 1997). . . 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.''

Wade and Goodnight's (1998) characterization of our views is clearly incompatible with statements such as (Coyne et al. 1997, p. 655):

> We may find evidence—and we do—that genetic drift can successfully oppose natural selection. This demonstrates that drift may play a role in adaptation, an idea for which we have surprisingly little evidence. The finding of important epistasis for fitness has implications for the reversibility of evolutionary change, and observations of population structure have implications for the possibility of local adaptation and sympatric speciation. While not completely supporting the SBT, such findings could nevertheless expand our view of evolutionary change beyond Fisher's scheme of directional selection operating in very large populations. In the following discussion we will call attention to cases in which *components* of the SBT have been found by observation and experiment.

Unlike Wade and Goodnight and Wright, we did not rely on verbal assertions about the relationship between drift, population subdivision, epistasis (for fitness), and pleiotropy that is required by the SBT. Instead, our critique included an explicit mathematical model that incorporates all of these forces (Coyne et al. 1997, pp. 647–648 and Appendix 1). This simple model reveals critical weaknesses of the SBT, including its requirement that selection, drift, and migration be finely balanced to produce all three phases of the process. Moreover, we have never claimed that fitness is independent of space and time. In fact, we emphasized the role of environmental fluctuations in producing ''peak shifts'' by selection alone, without the need for drift to carry populations through adaptive valleys (see Fear and Price 1998). We deny Wade and Goodnight's claim that the LST reflects our views of evolution.

We do not want to debate at length the difference between Fisher's and Wright's views of evolution. Our main concern is to critically examine evidence for the SBT, not to impugn that theory by defending Fisher. We question the value of Wade and Goodnight's notion that groups of ideas labeled ''Fisher'' and ''Wright'' must compete for our allegiance. The validity of the SBT—or of any evolutionary theory—does not depend on the winner of a population-genetic election in which one must choose between the slates of two flawed candidates. All evolutionists agree that both Fisher and Wright made enormous contributions to our field and that both occasionally made mistakes. Rejecting the SBT does not require embracing Fisher's views on population structure or speciation any more than it requires embracing his specious views of human history (Fisher 1958a, ch. XI) or his attacks on early studies indicating that smoking causes cancer (Fisher 1958b,c).

We have only two comments about the difference between Wright's and Fisher's views of evolution. First, whatever Fisher's views of the evolutionary significance of epistasis, he clearly did not ignore it. For example, Fisher (1918, pp. 408–409) explicitly discussed epistasis and made an important distinction between the biological reality of complex epistasis and the statistical importance of epistatic terms involving interactions among three or more loci. Similarly, Fisher (1958a, pp. 116–118) discussed the possible importance of two-locus epistasis for the evolution of recombination rates. Recent discussions of Fisher's ''fundamental theorem of natural selection'' have dealt with the role of epistasis in Fisher's highly compressed original treatment (e.g., Ewens 1992; Castilloux and Lessard 1995). Fisher (1918, pp. 408–409) made clear a crucial distinction between two consequences of epistasis: (1) it makes the marginal (i.e., additive) effect of an allele dependent on the genetic background; and (2) in each generation it causes deviations from a strictly additive model by generating additive-by-additive components of variance, maintaining linkage disequilibrium, and so on. Thus, while Fisher largely neglected epistatic contributions to the genetic variance (see Fisher 1918, p. 432), this does not imply that he supposed the additive components of gene action to be fixed quantities, independent of the state of other genes.

Second, Wade and Goodnight's claim that the primary goal of Wright's SBT was ''explaining the origins of adaptive novelty, whereas for Fisher it was explaining the refinement of existing adaptations'' (1998, p. 1540) is incorrect. As we noted (Coyne et al. 1997, p. 644), Wright himself said that the SBT creates ''the most favorable conditions for a continuing evolutionary process'' (Wright 1940b, p. 181) and ''this shifting balance process . . . has been the principal basis for evolution under exclusively biparental reproduction'' (Wright 1978, p. 524). In the four volumes of Wright's *Evolution and the Genetics of Populations,* it is hard to find a single experiment or observation, no matter how trivial, that is not construed as supporting the SBT. Anyone who has read Wright's work will realize that the SBT was seen not as an occasional process producing major evolutionary change, but as a general theory of *all* adaptation.

Wade and Goodnight's Case for the Shifting Balance Theory

Instead of addressing our criticisms of the SBT and the experiments that supposedly support it, Wade and Goodnight

(1998) defend the theory by making a separate argument for each of its components. They assert that: (1) ''group selection'' exists in nature; (2) such selection can be demonstrated to alter populations in the laboratory; (3) epistasis is found in some genetic analyses; (4) some studies reveal multiple ''fitness peaks''; (5) most species are subdivided into ''metapopulations''; (6) subdivided populations may behave differently from large panmictic ones; (7) additive genetic effects depend on a population's environment and genetic constitution; (8) theory suggests that drift can be important in ''converting'' epistatic into additive variance, in leading to interference between linked favorable alleles and in inflating genetic variance, thereby raising or even eliminating the valleys between peaks in the surface of mean fitness; and (9) Wright's SBT provides a more natural explanation of speciation than does Wade and Goodnight's LST theory.

These observations, even if all were true, are not a coherent defense of Wright's theory, which invokes a specific *concatenation* of drift, selection, and differential migration. In this case, support for the whole is considerably weaker than the sum of support for the individual parts. Moreover, several components of Wade and Goodnight's argument are deeply flawed.

Group Selection and the Shifting Balance Theory

Wade and Goodnight (1998) cite many field and laboratory studies that, in their view, demonstrate the power of group selection, and assert correctly that almost none of these studies were cited by Coyne et al. (1997). We were, in fact, aware of most of this work, but, for reasons given below, felt that almost all of it was irrelevant to our arguments. However, we did discuss in detail the study of Wade and Goodnight (1991), pointing out that its conclusions are questionable (see below). Wade and Goodnight have still not defended their claim that this experiment supports the SBT.

Most of the ''group selection'' studies cited by Wade and Goodnight (1998) are not useful in assessing the importance of the SBT because there is little, if any, connection between the specific role that differential migration plays in phase III of Wright's theory and the wide range of phenomena that Wade and Goodnight proffer as evidence for group selection. Throughout Wright's work, from 1931 through 1977 (chs. 12–13), his primary intention was to understand the evolution of adaptations favored by *individual* selection. Interactions among relatives could be important for some traits (e.g., Wright 1977, pp. 419, 446), but his emphasis was on general aspects of the evolutionary process (Wright 1977, p. 446) and the importance of considering epistasis and drift as well as natural selection. Although Wright mentions both selection among families and ''among local populations by asymmetric diffusion'' (Wright 1977, p. 446), the peaks and valleys of the mean fitness surfaces in his examples exist because of epistatic interactions *within* individual genotypes, not interactions *between* genotypes. Wright's concern was with contrasting ''mere selection according to the net effects of alleles'' with ''selection of genetic systems as wholes'' (Wright 1945, p. 416). Migration and drift allow individual populations to move from lower to higher adaptive peaks, and populations comprising individuals with more favorable multilocus genotypes (and thus higher mean fitness) would, he claimed, produce more emigrants than would populations stranded on lower adaptive peaks. This differential migration is the specific form of ''group selection'' invoked in phase III of the SBT.

In contrast, the list of field studies of ''group selection'' presented by Wade and Goodnight (1998) nearly all involve interactions among relatives (e.g., Frank 1985; Breden and Wade 1989; Herre 1993, 1995; Wade 1994; Stevens et al. 1995; Kelly 1997) and not better group performance based on higher fitness of individuals. Wade and Goodnight (1998) make almost no attempt to relate their examples of group selection to the specific assumptions of the SBT. Consider Herre's (1993) demonstration that, when transmitted vertically, nematodes that parasitize fig wasps have less impact on the fitness of the wasps than do parasites transmitted horizontally. Although this does involve groups of nematodes in individual figs, adaptations associated with vertical transmission have no obvious connection to the SBT because they can spread without genetic drift. Similarly, the kin-selected plant phenotypes that seem to be favored in populations with little dispersal (Kelly 1997) may illustrate the importance of structured populations, but they do not support the SBT. Again, such characters will spread without the need for genetic drift to overcome selective barriers.

We argued that many factors influence the relative success of different adaptive peaks, and Wrightian group selection between alternative peaks is likely to be weak compared to other forces. Under individual selection alone, the simplest assumption is that emigration from a deme is proportion to its mean fitness; the additional emigration produced by a peak shift then has a negligible effect on the spread of the new adaptive peak (Barton and Clark 1990; Rouhani and Barton 1993). As discussed in Rouhani and Barton (1993), differential emigration may be amplified by interactions between individuals (so that the rate of emigration becomes proportional to mean fitness raised to some power, γ), but this amplification must be extreme (i.e., γ significantly greater than one) to have a significant effect on the spatial spread of adaptive peaks. Although fitter peaks may spread over space even without differential migration, they can be trapped by barriers to dispersal or thwarted by sundry ecological factors. In addition, it is difficult for the shifting balance process to assemble complex adaptations from multilocus genotypes fixed in different local populations (Coyne et al. 1997, p. 654). Finally, Wright's assertion that higher individual fitness would lead to ''a greater surplus population . . . and excess dispersion'' is neither self-evident nor supported by evidence. Explicit models of density-independent selection in density-regulated populations show that selection can decrease as well as increase population size (Prout 1980; Fear and Price 1998).

Wade and Goodnight (1998) cite several studies showing that populations will respond to group selection. However, this work does not support the SBT because *any* character exhibiting additive genetic variance will respond to selection, whether one selects individuals or *groups* of individuals whose means deviate in the desired direction. One could, for example, easily increase bristle number in *Drosophila* by breeding from individual flies having the most bristles or by breeding from those *groups* of flies having the highest mean

bristle number. Likewise, ''family selection,'' as practiced in Muir's (1996) study of egg-laying in domestic chickens, is a well known method of animal breeding that is used to alter traits of low heritability because it effectively reduces environmental variance and allows selection for traits that cannot be scored in all individuals (Falconer and Mackay 1996, ch. 13). Various forms of kin and trait-group selection may indeed explain some important adaptations in nature (Hamilton 1972; Wilson 1980), but these processes do not offer general support for the SBT. As noted above, many of them would allow the deterministic spread of ''group selected'' traits from low frequency without the need for drift to drive populations through adaptive valleys.

Individual selection may sometimes be more rapid in subdivided than in panmictic populations (as when selection acts on traits based on advantageous recessive alleles) because selection can operate more rapidly when inbreeding increases the frequency of the advantageous phenotype (e.g., Caballero et al. 1991). Again, this requires neither the crossing of adaptive valleys nor differential migration between populations.

Wade and Goodnight (1998) also note that ''group selection'' has been detected by ''contextual analysis'' (e.g., Stevens et al. 1995). This technique, which was introduced by Heisler and Damuth (1987) and elaborated by Goodnight et al. (1992), involves partitioning levels of selection by regressing a component of fitness onto different phenotypes, including not only the phenotypes of individuals, but also ''group traits'' that encompass either mean phenotypes of groups (averaged across constituent individuals) or true group properties such as density. A regression that yields a significant effect of a ''group trait'' is considered to demonstrate group selection.

This approach has serious limitations. If groups vary in density for ecological reasons alone, such analysis will detect ''group selection'' when in reality there is only density-dependent reproduction. Specious group effects can also arise when phenotypic differences among groups are based on *nongenetic* factors, as when local environmental conditions produce developmental modification of the phenotype (Price et al. 1988; Rausher 1992). Finally, contextual analysis may reveal that selection acts in the same direction on individuals and on groups (Stevens et al. 1995). In such cases, population structure is not required for the fixation of adaptive traits and thus offers little support for the SBT.

We leave it to others to debate the definitions of group selection and the importance of this process in evolution (for a review of the major issues, see Lloyd 1994, chs. 4–5). However, we believe that the time is ripe for a critical review of the many studies of ''group selection.'' As Coyne et al. (1997) noted, such selection must certainly operate under some circumstances. Wade and Goodnight's (1998) examples of group selection, however, subsume a variety of phenomena, many of which can fix adaptations in a species without the crossing of adaptive valleys or differential migration based on enhanced *individual* fitness of the kind invoked by Wright.

Two studies, those of Craig and Muir (1996) and Muir (1996), bear closer inspection because of Wade and Goodnight's claim that they show group selection to be more effective than individual selection: ''In the latter study, intergroup selection [for egg-laying rates in domestic chickens] was able to achieve a 30% increase where long-term mass selection had failed'' (Wade and Goodnight, p. 1538). An examination of these papers shows that this claim is incorrect.

Muir (1996) selected for the total mass of eggs produced over a year by isolated cages of hens, each containing nine full sisters. (This is, of course, family selection.) The selection response was compared to that of an *unselected* control line (not, as Wade and Goodnight [1998] claim, to a line subject simultaneously to individual selection). The aggression among caged hens initially caused serious injuries, mortality, and an egg-laying rate far below that of the unselected control. However, after six generations of selecting from the most productive cages, the egg-laying rate of families rose to nearly that of the unselected control. This increase was due to an improvement in the survival of caged hens accompanying a reduction in beak-inflicted injuries (Craig and Muir 1996).

Family selection for more amiable chickens therefore raised egg production to near control levels. However, there was no comparison to the results of *individual* selection because control hens were kept in individual cages, where aggression was not possible. ''Long-term mass selection'' therefore had not failed—it had not been practiced at all. The problem is identical to that of Wade and Goodnight's (1991) experiment selecting for increased productivity in flour beetles. Here, the authors also claimed that group selection produced a greater response than did individual selection. This conclusion is again questionable because no individual selection was practiced (Coyne et al. 1997, pp. 663–664).

Thus, we find no experimental evidence for Wright's claim that group selection—except as ''family selection'' on traits with low heritability (Falconer and Mackay 1996, ch. 13)—can be faster and more efficient than individual selection.

Population Structure, Epistasis, ''Conversion'' of Variance, and the Shifting Balance Theory

Spatial structuring of populations is, of course, important in evolution (e.g., Wilson 1980; Hedrick 1986). However, accepting that most species are spatially structured does not in itself support the SBT. Likewise, the fact that mass selection depends only on additive genetic variation does not mean that dominance and epistasis are unimportant in determining the outcome of such selection or the production of phenotypes. Parent-offspring regressions depend explicitly on additive-by-additive and higher-order additive interactions between loci, and such epistatic effects contribute directly to mass selection response (e.g., Bulmer 1980, pp. 160–162). It is simply not the case that in ''all evolutionary discussion, the additive and epistatic components of genetic variation are considered separate and distinct entities . . . Most often, strictly additive models with no epistasis are investigated'' (Wade and Goodnight 1998, p. 1538). It is, in fact, widely appreciated that epistasis makes the additive effects of genes conditional on genetic background (e.g., Lynch and Walsh 1998, p. 87). Even in idealized quantitative genetic models that assume fixed effects of alleles on particular traits (e.g., Turelli and Barton 1994), the goal is to understand the evolution of these traits under nonlinear forms of selection that introduce epistasis—and thus genotype-dependent allelic

effects—with respect to fitness. As we emphasized in Coyne et al. (1997, pp. 646–647), Wright's discussions of the SBT focused on simple models in which epistasis *for fitness* is produced by nonlinear selection acting on additively determined traits.

Wade and Goodnight (1998, p. 1544–1545) argue that, with epistasis and population subdivision, the ranking of breeding values may vary from place to place. However, this does not imply that mass selection will be ineffective, nor does it address the difficulties that populations face in crossing adaptive valleys in opposition to natural selection. There is a substantial difference between accepting that epistasis is widespread and accepting that it traps populations at alternative fitness peaks (Whitlock et al. 1995).

Wade and Goodnight (1998, pp. 1538–1539) emphasize the importance of ''conversion'' of nonadditive to additive genetic variance. Some experiments do indeed show that additive genetic variance can increase following a population bottleneck. This might facilitate divergence by increasing the subsequent response to selection or by generating extreme but advantageous phenotypes. However, there has been little critical assessment of just how an increase in additive variance could aid subsequent divergence of populations. First, many instances of ''conversion'' may represent only increases in the frequency of rare recessive alleles; that is, the conversion of *dominance* to additive variance. Because these alleles are likely to be deleterious, most will be eliminated by selection following the bottleneck (Barton 1989a; Willis and Orr 1993; Lopez-Fanjul et al. 1999). In addition, additive variance can be inflated by epistasis only under restrictive conditions (Lopez-Fanjul et al. 1999). Finally, the probability of a peak shift after a population bottleneck depends primarily on the *net variance in the trait mean,* rather than the increase in trait variance; and the former is unlikely to be greatly increased through ''conversion'' (Barton 1989a). To demonstrate a role for ''conversion'' in the SBT, one requires theoretical or empirical evidence that such conversion of variance increases the probability of peak shifts.

Wade and Goodnight's Views of Speciation

We are especially concerned with Wade and Goodnight's (1998) unusual views of speciation, as they run counter to facts and ideas that have recently produced substantial progress in this field. Wade and Goodnight contend that evolutionists who do not support Wright's SBT: (1) do not accept the reality of epistasis and thus cannot logically invoke Dobzhansky's (1936) classic epistasis-based model for the development of postzygotic isolation; and (2) must accept an alternative model of speciation, which they attribute to Fisher—a model that has not appeared in a single major paper during the last two decades of intensive work on this subject.

Wade and Goodnight's (1998) discussion of competing theories of speciation is rather unclear. Their first theory—the one that they favor—we call ''Wrightian speciation.'' This involves a shifting balance process in which initially maladaptive and epistatic gene combinations become fixed by drift within a subdivided species, thus causing postzygotic reproductive isolation in hybrids with other populations.

We call their alternative theory, which Wade and Goodnight (1998) derive from Fisher's supposed views, ''LST speciation.'' However, Wade and Goodnight cause some confusion by giving two contradictory characterizations of this theory. In the first (p. 1547), LST speciation results from ecological isolation that eventually develops between allopatric populations exposed to different environments. When such taxa become secondarily sympatric, they are different species because the hybrids are ecologically unfit (a form of postzygotic isolation). However, they then note that this theory does *not* include the idea that hybrid inviability or sterility can result from from deleterious epistatic interactions occurring during development: ''there is immense interest in speciation genetics and abundant data attesting to the role of gene interaction in reproductive isolation . . . but no consideration of epistasis in the LST'' (p. 1549).

In other places, however (e.g., p. 1548), Wade and Goodnight admit that after LST speciation some hybrid sterility or inviability may result not from ecological divergence, but from inherently deleterious interactions between genes of different taxa. Such interactions, however, are characterized as ''entirely ad hoc'' (p. 1547).

To avoid the confusion between these dichotomous views of LST speciation, we will call ''LST speciation'' the nonepistatic version described in Wade and Goodnight (1998, pp. 1547,1549) and coin the term ''synthetic speciation'' to characterize the alternative model of speciation that includes epistasis but no drift-induced peak shifts.

The ''synthetic theory of speciation,'' largely neglected by Wade and Goodnight, is in fact the view of speciation most widely accepted by modern evolutionists. As proposed by Dobzhansky (1936, 1937), Muller (1940, 1942), Mayr (1942, 1963), and others, this theory holds that most forms of postzygotic isolation are indeed products of epistasis, but that the relevant epistatic interactions are realized only in hybrids. This epistasis results from deleterious interactions between different alleles fixed by natural selection or genetic drift in geographically isolated populations.

Wade and Goodnight's ambiguous discussion of ''LST speciation'' illustrates the artificiality of any attempt to polarize studies of adaptation and speciation into ''Fisher'' versus ''Wright'' camps. In fact, neither Fisher nor Wright made significant contributions to the development of the synthetic theory of speciation (Orr 1996). The classic model of ''synthetic speciation'' is the Bateson (1909), Dobzhansky (1937), and Muller (1942) two-locus example described in Coyne et al. (1997, p. 651). In this model, postzygotic isolation in interspecific hybrids results from deleterious interactions between alleles that have never been ''tested'' together in a common genome. Such epistasis need not occur within either of the evolving taxa: It is a phenomenon that arises only when taxa are hybridized. Therefore, the evolution of such incompatibilities does not require structured populations or the crossing of adaptive valleys. A good example is the case of monobrachial chromosome fusions (Bickham and Baker 1980). Fusions between single chromosomes often cause little or no sterility in heterozygotes and can be fixed within a species by positive selection or drift. However, if chromosome P fuses with chromosome Q in one population, but with chromosome R in an isolated population, severe meiotic problems may occur when four different chromosomes try to

pair in the hybrids. Strong postzygotic isolation has thus appeared in hybrids, but not within either species.

We are not sure why Wade and Goodnight repeatedly characterize between-species epistasis as an ''ad hoc'' assumption, but it cannot be because such interactions have only recently been added to theories of speciation. Deleterious epistasis occurring within hybrids but not within pure species was part of the synthetic theory of speciation from the outset (Orr 1996). As early as 1909, well before Fisher had published his first paper on evolutionary biology (and in the absence of any direct experimental evidence), Bateson recognized that interspecific gene interactions were a priori necessary for postzygotic isolation. Muller (1940, 1942), apparently unaware of Bateson's (1909) precedent, proposed an important role for epistasis in hybrid sterility and inviability based on direct observations of mutations in *Drosophila.* The synthetic theory of postzygotic isolation, as formalized and popularized by Dobzhansky, Mayr, and Muller, has been an uncontroversial view of evolution for over half a century.

The overriding problem with Wade and Goodnight's view of speciation is the notion that hybrid incompatibilities result from genes causing similar incompatibilities *as they become fixed within a species,* and that this fixation involves a shifting balance process. This leads to their assumption that studying *intraspecific* variation in genes affecting the fitness of intraspecific hybrids will reveal the genetics underlying the breakdown hybrids between distinct species. But speciation must involve more than just the sorting into descendant lineages of ''reproductive isolation'' alleles segregating in an ancestor. As Weber (1996, p. 212) noted, ''Certainly the complex interaction systems of pigs and camels would not have been present already in the first artiodactyl gene pool.''

It is clear that speciation must usually begin with the fixation of alleles segregating in an ancestral gene pool, followed by the fixation of newly arising mutations in geographically isolated populations. However, there are several reasons why postzygotic isolation in hybrids is likely to result not from genes segregating in an ancestor, but from newly arising mutations that are differentially fixed among descendants and that cause deleterious interactions only in hybrids (for a description of the accumulation of these incompatibilities, see Orr 1995). First, genes that cause hybrid sterility or inviability seem to have no deleterious effects in pure species (see below). Second, if ''Wrightian speciation'' were correct, one would expect to see the evolution of substantial reproductive isolation among inbred lines isolated in the laboratory, for such lines could arrive at different adaptive peaks and produce maladapted hybrids. Yet such observations are almost nonexistent: incipient species have not been created in the laboratory in this way (Thomson 1986). Thousands of isofemale lines and inbred strains have been created in *Drosophila,* for example—constituting the ''many small experiments'' of Wade and Goodnight's title—but none of these (with the possible exception of Dobzhansky and Pavlovsky 1966) has become a new species with full postzygotic isolation. One might argue that ''Wrightian speciation'' occurs by steps, so that numerous rounds of the shifting balance process would be required to attain complete reproductive isolation, but this makes the process exceedingly slow. Finally, recent work on Haldane's rule (the generalization that if only one sex is inviable or sterile in hybrids, it is the heterogametic sex; Haldane 1922) shows that the synthetic theory of speciation explains the data far better than does the view that postzygotic isolation results from deleterious alleles fixed within species by the shifting balance process.

To draw this contrast, it is useful to consider Wade and Goodnight's (1998) analysis of Haldane's rule. They begin their discussion by following the statement of the rule (Haldane 1922) with what appears to be an attempt at explaining it: ''Haldane's rule 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 heterogametic sex'' (Wade and Goodnight 1998, p. 1549). The end of this quote leaves us uncertain which, if any, proposed explanation of Haldane's rule Wade and Goodnight support, but we disagree sharply with their suggestion that we should try to understand the causes of Haldane's rule by studying intraspecific variation.

Recent experimental and comparative analyses of interspecific incompatibilities have advanced our understanding of Haldane's rule and of the genetics of postzygotic isolation (e.g., Coyne and Orr 1989; Orr 1993b; True et al. 1996; Turelli and Begun 1997; Presgraves and Orr 1998; Sasa et al. 1998; Ting et al. 1998). These analyses have supported two complementary explanations of Haldane's rule, both involving epistasis only in hybrids: the ''dominance theory'' (Muller 1940, 1942; Orr 1993a; Turelli and Orr 1995) and the ''faster male'' theory (Orr 1989; Wu et al. 1996; Presgraves and Orr 1998; Turelli 1998; see also the reviews by Laurie 1997; Orr 1997). In contrast to these approaches, Wade and Goodnight propose that the key to understanding this rule lies in considering *intraspecific* variation in hybrid performance. They criticize the ''dominance theory'' by arguing that: ''the dominance hypothesis . . . 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'' (p. 1547). However, these data say nothing about the value of the dominance for interpreting the genetics of *interspecific* postzygotic isolation, as the dominance theory deals specifically with interactions between alleles that almost never segregate in the progenitor species. Thus, the data that Wade and Goodnight cite are better interpreted as evidence against their view that the key to understanding postzygotic isolation between species is to study variation in hybrid performance within a species.

The sole evidence cited by Wade and Goodnight (1998) to support ''Wrightian speciation'' is that some populations and genotypes of *Tribolium castaneum* differ in the degree of inviability and morphological abnormalities that they generate in hybrids with a related species, *T. freemani* (Wade and Johnson 1994; Wade et al. 1997). These observations, however, show only intraspecific variation at genes causing postzygotic isolation in hybrids *between different species.* There is no evidence that these genes cause any fitness problems *within* a species.

The lack of congruence between the genetics of intraspecific

variation and of interspecific differences is hardly surprising in light of the time scale—on the order of 10^6 years—over which Haldane's rule typically appears (Coyne and Orr 1989, 1997; Turelli and Begun 1997). The genetic differences accumulating over such times are not just a reshuffling of alleles present in the ancestral species, but also reflect the fixation of many new mutations. The voluminous data on molecular evolution show that many substitutions, both neutral and adaptive, are expected over such periods (Gillespie 1991).

Nevertheless, there are other intraspecific variants, similar to those described in *Tribolium castaneum,* that affect the appearance or severity of postzygotic isolation in hybrids with another species. But these variants do not conform to the behavior predicted by Wade and Goodnight (1998): they cause *no* incompatibilities when segregating within species, but were detected only after interspecific hybridization. Classic studies include *Drosophila aldrichi* and *D. mulleri,* (Crow 1942), *Crepis tectorum* and *C. capillaris* (Hollingshead 1930), and the cottons *Gossypium barbadense* and *G. hirsutum* (Stephens 1950). Additional examples are given by Dobzhansky (1951, pp. 199–202) and Orr (1997, pp. 202–203). Moreover, work on the six known ''hybrid rescue alleles'' in *Drosophila* (variants within a species that restore the viability of normally inviable interspecific hybrids) give results flatly inconsistent with Wade and Goodnight's claim (Hutter 1997 and references therein). Five of these alleles are found in natural populations, and the effects of all six are manifested *only in hybrids.* Intensive genetic analysis has revealed no detectable within-species incompatibilities caused by either rescuing or nonrescuing alleles (Sawamura and Yamamoto 1993, 1997; Sawamura et al. 1993a,b,c).

These studies, which are not mentioned by Wade and Goodnight, show that alleles that are benign within a species can have severely deleterious effects in hybrids. Indeed, the marshaling of such strong and such convincing evidence for synthetic speciation has been called ''the single most important result of the past decade of work on the genetics of speciation'' (Orr 1997, p. 202).

Wade and Goodnight assert that the evolution of postzygotic isolation is likely to be very slow during LST or synthetic speciation because of the rarity of adaptive mutations and the ''additional time necessary for the fixation of the mutations by random drift or natural selection'' (p. 1548). This claim and the equivalent claim of Wright that mass selection is too slow to explain adaptive evolution are unsupported. Under the synthetic theory, the waiting time to postzygotic isolation depends not only on the rate of adaptive substitution, but also on the probability that any two alleles will be incompatible when brought together in hybrids (Orr 1995). In only a handful of species do we have information on either of these parameters (e.g., Vacquier 1998). Nor have Wade and Goodnight made any calculations to show that LST or synthetic speciation are too slow to account for the diversity of existing species, which would be the only convincing way to buttress their claim. We know that postzygotic reproductive isolation can sometimes evolve rapidly (Christie and Macnair 1984; Ting et al. 1998), but usually evolves slowly (Wilson et al. 1974; Prager and Wilson 1975; Coyne and Orr 1997; Sasa et al. 1998). We expect that Wrightian speciation, if it occurs, would usually be slow because it requires the successive fixation of at least several deleterious mutations by genetic drift and the spread of adaptive peaks through structured populations.

The possibility that Wrightian speciation can be glacially slow is demonstrated by work on the theory of chromosomal speciation, which proposes that postzygotic isolation results from the fixation in separate populations of deleterious chromosome rearrangements that subsequently produce abnormal meiosis in heterozygous hybrids. Like Wrightian speciation, this process involves small population sizes that allow drift to cause genetic change opposed by selection. After reviewing the data supposedly supporting this scenario, Futuyma and Mayer (1980), Sites and Moritz (1987), and Coyne et al. (1993) conclude that there is little evidence for chromosomal speciation unless the postzygotic isolation was caused by several rearrangements that were *not* individually deleterious. Chromosomally based postzygotic isolation clearly evolves more readily when, as in the case of monobrachial fusions, populations do not have to cross adaptive valleys. Wright's (1941) analysis of chromosome evolution via genetic drift and its subsequent theoretical elaboration by Lande (1979) and Walsh (1982) show the process to be exceedingly slow when it involves peak shifts, because the probability of such a shift decreases exponentially with $N_e s$ (where N_e is the effective population size and s is the selective disadvantage of the heterozygote). Reproductive isolation under Wright's (1935) model of stabilizing selection on a quantitative trait also evolves very slowly (Barton 1989b). (We should note that although we are discussing here the difficulty and slowness of peak shifts, our primary problem with the SBT has always been the difficulty of achieving phase III—the spread of adaptations after peak shifts have already occurred.)

Wade and Goodnight (1998) criticize the Fisherian and synthetic theories of speciation for their lack of mathematical underpinnings: ''the connection between microevolution under Fisher's LST and speciation will remain indirect, ad hoc, and qualitative until formal epistatic models are developed'' (p. 1548). However, such models already exist. Indeed, Wade and Goodnight cite two of them: Turelli and Orr (1995) and Orr and Orr (1996). These models, which extend the work of Orr (1993a, 1995), are built on the Bateson-Dobzhansky-Muller synthetic view of speciation. It is ironic that Barton (1989b) may have provided the only mathematical model of multilocus reproductive isolation based on the SBT. Wright's only two papers on this topic (Wright 1940a,b) offer no mathematics, but only verbal arguments for the SBT.

Considering all this work, we do not see why speciation should occur more rapidly under the Wrightian than under the synthetic theory of speciation. Given the paucity of data (apart from polyploid speciation) indicating rapid evolution of postzygotic isolation, we do not understand Wade and Goodnight's concern with these relative rates.

Finally, Wade and Goodnight (1998) appear to believe that incompatibilities resulting from Wrightian speciation are required for *all* forms of reproductive isolation, not just hybrid sterility and inviability: ''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 . . . . 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'' (p. 1549). Here Wade and Goodnight confuse speciation with hybrid sterility and inviability. Speciation, however, involves more than just postzygotic isolation. Most forms of *prezygotic* isolation, for example, do not involve intrinsic genetic incompatibilities in hybrids, but rather features such as temporal differences in breeding, ecological differences, or divergence in sexual behavior, pheromones, pollinators, or morphology that cause assortative mating.

Have Wade and Goodnight Advanced the Case for the Shifting Balance Theory?

Wade and Goodnight (1998) defend the SBT by showing that the ''large population size theory,'' which they attribute to Fisher and to Coyne et al. (1997), does not deal with epistasis or with subdivided populations, which are pervasive features of the real world. They offer laboratory and field evidence that selection may operate differently in structured and in panmictic populations, that populations are often subdivided, and that epistasis is widespread. Finally, they present a discussion of speciation that ignores the consensus model for the evolution of postzygotic reproductive isolation. They conclude that because elements of the SBT can be seen in nature or the laboratory, the entire theory remains plausible as an explanation of adaptation.

Although evidence can be found for each component of the SBT, we have found no cases of evolution in which all components work simultaneously, and no support for Wright's contention that the SBT provides a general explanation of adaptation. We emphasized that the main difficulty is not envisioning how populations might shift between adaptive peaks, but rather how these populations could spread so as to favor adaptive peaks that are in some sense ''fitter.'' Only then could the shifting balance process contribute to adaptation in the way proposed by Wright. Moreover, we feel that the complexity of the SBT makes it nearly untestable. This may explain why few people besides Wright have cited specific adaptations in nature that might have resulted from a shifting balance process. In our previous paper (Coyne et al. 1997, pp. 664–665), however, we describe several approaches for testing the likelihood of this process in nature, including studies of chromosomal speciation and of the loss of fitness in crosses between geographic populations of a species (''outbreeding depression'').

However, we do have many examples of adaptation by simple mass selection. For example, nobody has invoked the SBT to explain classic examples of microevolution such as the evolution of heavy metal tolerance in plants (Macnair 1981), body size evolution in natural populations of *Drosophila* along latitudinal gradients (Partridge and Coyne 1997), bill and body size evolution in the Galapagos finches (Grant 1986), or the evolution of color patterns, life histories, and behavior of guppies responding to the pressures of predation and sexual selection (Endler 1980; Reznick et al. 1990; Magurran et al. 1992). Endler (1986) gives a long list of other examples. In contrast, Wade and Goodnight (1998) offer not a single example of an adaptation in nature that probably arose by Wright's shifting balance process.

Response to Peck et al.

Peck et al. (1998) model the third phase of Wright's SBT by simulating the spread through a two-dimensional habitat of an allele that decreases fitness when heterozygous, but increases fitness when homozygous. These simulations show that the allele can spread out from a single deme even when selection and migration are strong ($Ns >> 1$, $Nm >> 1$). Peck et al. (1998) argue that this is because the third phase is facilitated by isolation by distance and by stochastic migration, which are not included in previous theoretical treatments. We disagree.

First, Peck et al. (1998, table 1) claim that there have been no theoretical analyses of the SBT in spatially extended populations. However, Rouhani and Barton (1987)—in a paper cited by Peck et al. (1998)—use a model of disruptive selection on a quantitative trait to show that a new peak can increase and spread through a continuous population. In two dimensions, this process gives a strong advantage to the fitter peak and can proceed most efficiently when neighborhood size is intermediate. This theory was extended by Barton and Rouhani (1991) to a model incorporating heterozygote disadvantage. That paper differs from Peck et al.'s only in that it does not include stochastic migration. Barton and Rouhani (1991) give results for a larger habitat, and provide an analytic framework that can be extrapolated to a wide range of parameters. At the very least, Peck et al. must show that, in the absence of stochastic migration, their simulations are consistent with the scaling relations derived by Barton and Rouhani (1991) and must demonstrate how stochastic migration alters those relations.

Peck et al.'s (1998) grid of 7×7 demes is almost certainly too small to approach the two-dimensional limit considered by Barton and Rouhani (1991); when selection is weak, the set of demes should behave as a panmictic population, and when migration is low, demes will be fixed for one or the other allele (Slatkin 1981; Lande 1984). Although not enough detail is given to allow a quantitative comparison, their simulation results are qualitatively as expected and so do not add support for the SBT. In particular, an allele that is initially fixed in one deme can spread deterministically (i.e., when Nm and $Ns >> 1$), provided that migration can swamp selection (cf. Crow et al. 1990; Barton 1992). With the fitnesses assumed by Peck et al. (1998),

$$\frac{1}{1 - s} : 1 - s : 1,$$

the fitter homozygote can spread from one deme to another if $m/s > 0.087$ (Lande 1984); this result should also apply approximately to the spread of a single peak throughout two dimensions. However, if Nm is large, the favorable allele is unlikely to reach high frequency—this is why Nm must be intermediate for the SBT as a whole to operate (Appendix 1 of Coyne et al. 1997). Peck et al. (1998) considered the rapid spread observed for large Nm and Ns ''unexpected given Barton and Rouhani's (1993) results.'' However, the latter paper considered the *island model*, in which fixation of a single deme has negligible effect on the population as a whole. The relevant comparison is with Barton and Rouhani's (1991) results for a two-dimensional population.

Second, Peck et al. (1998) invoke stochastic migration as favoring the SBT. Assuming that a finite (and therefore random) number of individuals migrate introduces an additional source of noise, making random peak shifts more likely in a population of a given mean size. However, Peck et al. provide no comparison between simulations with and without stochastic migration, and so it is unclear what effect such migration might have. A better comparison might be between parameter values that give the same level of random drift (measured, say, by effects on neutral alleles). Stochastic migration does have an effect different from that of random drift, in that the former process increases the variance in allele frequency even when loci are close to fixation (see eq. A2 in our Appendix); and so such a comparison might reveal effects relevant to the SBT.

Instead of comparing computer simulations with and without stochastic migration, Peck et al. (1998) consider a one-dimensional diffusion approximation with and without stochastic migration. However, the diffusion analysis given in their appendix 2 is incorrect, and the results they present are artifacts of their error. In our Appendix (see below), we show that when m and s are small (so that the diffusion approximation applies), stochastic migration has a negligible effect and cannot aid the SBT.

In many cases, the simulations of Peck et al. (1998) involve large m and s, in which case stochastic migration could conceivably contribute to peak shifts. Several studies have shown that stochastic migration can have significant effects on patterns of genetic variation (e.g., Levin 1988; Epperson 1994; Gaggiotti and Smouse 1996). However, without the proper comparisons being made, it is impossible to know whether stochastic migration advances or retards peak shifts. Peck et al. (1998) provide no support for their conjecture that stochastic migration has a significant effect on phase III.

Existing theory and Peck et al.'s (1998) simulations both show that the SBT can operate in both island and two-dimensional population structures, and can give a substantial advantage to the fitter peak for certain ranges of parameter values. Regardless of whether or not Peck et al.'s conjecture that stochastic migration facilitates phase III proves correct, this still does not address our strongest criticisms of the SBT (Coyne et al. 1997, pp. 653–655). These were based not on these idealized models, but on the demonstration that random variation in density and dispersal can aid the spread of adaptive peaks, and also lead to their establishment without regard to their effects on fitness. For these reasons, the ''third phase'' of the SBT need not be adaptive. The effects of Wrightian group selection are weak, and therefore especially likely to be swamped by the vagaries of population structure. It is also hard for ''adaptive peaks'' established in different areas to be brought together in one population: the SBT suffers from limited opportunities for recombination. While Peck et al.'s (1998) simulation results seem consistent with existing theory (although a quantitative comparison with analytical predictions would be desirable), they do not address the theoretical weaknesses of the SBT emphasized in our review.

Final Remarks

The popularity of the SBT seems to rest on a kind of holism that deems the best theories to be those that include the greatest number of ecological and evolutionary forces. In the end, however, a theory prevails or fails based on its value in explaining the real world. We have one theory—selection on individuals—that is both simple and able to explain many examples of adaptation and reproductive isolation in nature. We have another theory—the SBT—that is complex, known to apply only under restrictive conditions, and has not proved a superior or necessary explanation for a single adaptation. To us, the choice is simple.

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Appendix

Here we demonstrate that the diffusion analysis of Peck et al. (1998) is incorrect. In their appendix 2, Peck et al. (1998) assume—as is usual in population-genetic diffusion approximations involving genetic drift—that the selection coefficient and average migration rate are proportional to the inverse of the population size. In this diffusion limit, terms of order $(1/N)^2$ and smaller are eliminated. That explains why the selection parameter does not appear in the infinitesimal variance, $\sigma^2(p)$, in their appendix 2. If we transform their expression for $\sigma^2(p)$ back to the original time scale, Peck et al. (1998) assert that the infinitesimal variance with stochastic migration is

$$\sigma^2(p) = \frac{p(1-p)}{2N} + \mathbf{m}, \quad \text{(A1)}$$

where **m** is the mean migration rate. The term **m** in (A1) vanishes with deterministic migration, and this is the only difference between the two diffusions that they compare in their figure 4. However, if we ignore selection, which we agree has no effect on the infinitesimal variance in the weak-selection limit, the exact expression for $\mathrm{Var}(p_{t+1} \mid p_t)$ is easily computed for their model as:

$$\mathrm{var}(p_{t+1} \mid p_t) = (1-\mathbf{m})^2\frac{p(1-p)}{2N} + (1-p)^2\frac{\mathbf{m}(1-\mathbf{m})}{N}. \quad \text{(A2)}$$

(The denominator in the second term is N rather than $2N$ because *individuals* are sampled after random mating in Peck et al.'s random migration model.) From this expression, it is obvious that if **m** is proportional to $1/N$ (as it must be to vanish from the term proportional to $p(1-p)$ in approximation 1 from Peck et al. 1998), then the second term in (A2), which describes the contribution from stochastic migration, is of order $(1/N)^2$ and hence negligible. Thus, in the conventional diffusion limit, $\sigma^2(p) = p(1-p)/(2N)$, irrespective of whether migration is stochastic or deterministic; and the results displayed in Figure 4 of Peck et al. (1998) are artifacts of their mathematical error. Unlike Peck et al.'s (1998) diffusion approximation for the effects of stochastic migration, ours agrees with Wright's (1977, p. 445, top equation). Nagylaki (1979) has shown that a different scaling of the migration parameter is needed for stochastic migration to alter the diffusion analysis. However, the resulting diffusion is qualitatively different from Peck et al.'s (1998).

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THE ONGOING SYNTHESIS: A REPLY TO COYNE, BARTON, AND TURELLI

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We wish to address some of the important issues raised by Coyne et al. (2000) in their critique of our Perspective on the contrasting views of Fisher and Wright (Wade and Goodnight 1998). Many of the points that they raise illustrate important differences between their view and ours on the content of evolutionary theory and on the experimental approaches used to test and investigate evolutionary hypotheses in laboratory and field studies. We believe that a controversy like this can be useful because it helps to identify gaps in the current understanding of evolutionary geneticists and to frame questions for future research. However, we also believe that, ultimately, it can be resolved only by continuing to collect more experimental data and by integrating the theoretical and empirical findings of the past 20 years more fully into existing thought. Only by broadening the range of data and types of experiments considered relevant can features like epistasis and population genetic structure be understood. By moving from parsimony to true understanding, we hope to resolve the differences between the two schools of thought, which have their roots in the Fisher-Wright debates (e.g., Provine 1971, Lloyd 2000).

Empirical studies cited in our Perspective have had a formative influence on our views of Fisher and Wright, the relationship between interdemic and group selection, and the role of gene interactions (epistasis) in evolution. As Coyne et al. (2000) point out, our 1998 paper, by design, is a ''Perspective'' and we do not respond directly to the specific objections to Wright's shifting balance theory (SBT) that they raised in an earlier paper (Coyne et al. 1997). Instead, we reexamine the theories of both Fisher and Wright in light of new theoretical findings and new empirical data gathered in the 60 plus years since the original theories were put forward. We conclude that *both* theories, at least in their idealized original versions, have difficulty incorporating important features of natural populations (see table 2 in Wade and Goodnight 1998) because of the assumptions that differ between them. We argue that this limits the application of each theory to different domains. We conclude that many of the recent theoretical and empirical findings are not, strictly speaking, explicit in either theory and can be viewed as ''enriching'' both of them, especially Wright's. Many of these recent findings were discovered by ourselves and our colleagues in attempts to evaluate more rigorously some of the ideas that Wright expressed only in words and also in attempts to provide an empirical foundation to the study of adaptive evolution in genetically subdivided populations. Our research programs are no different in this respect than efforts by Coyne and his colleagues to provide a better theoretical and empirical understanding of the genetic basis of Haldane's rule in order to understand speciation.

Data and arguments against the idealized version of Wright's SBT presented in Coyne et al. (1997) are of keen interest to us, but, overall, we find them too narrow in scope for a point-by-point reply. As evidenced by the lack of overlap in the Literature Cited sections of Wade and Goodnight (1998) and Coyne et al. (1997), they omitted much of what we con-