Letter to the Editor

Dominance and HALDANE's Rule

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Manuscript received January 10, 1996
Accepted for publication January 25, 1996

TWO commentaries on our analysis of HALDANE's rule (TURELLI and ORR 1995) appear in this issue. A third, by C.-I. WU, M. F. PALOPOLI and N. A. JOHNSON, was withdrawn after it and our response were accepted for publication. We briefly respond to the two published commentaries and address some of the issues raised by the third, under the assumption that several of the issues raised by WU *et al.* may also concern other readers.

ZENG's (1996) note clarifies ideas originally presented by ORR (1993a). As ZENG's conclusions are a subset of ours, there is no disagreement on which to comment. SAWAMURA (1996), on the other hand, worries that several exceptions to HALDANE's rule "are not explicable by a simple dominance theory." Although we doubt that these exceptions are so difficult to explain (see below), we do not understand why SAWAMURA believes that exceptions discredit our explanation of HALDANE's rule. We are obviously trying to explain the rule and, by definition, not the exceptions. In particular, although we posit that hybrid incompatibilities typically act as recessives, we do not claim that they *all* do. By analogy, the theories explaining why casinos are, as a rule, profitable are not disproved by those exceptional individuals who beat the house. Moreover, we agree with SAWAMURA that many of the exceptions to HALDANE's rule may involve maternal effects. Indeed, we agree so much that we discussed this possibility at length (TURELLI and ORR 1995, p. 395). We trust the reader will agree that our discussion of this idea—originally offered by WU and DAVIS (1993)—does not differ substantially from SAWAMURA's.

Several readers of our paper, including WU, PALOPOLI and JOHNSON, have raised two questions about the dominance theory: (1) why should the alleles causing hybrid problems act as recessives? and (2) can dominance explain HALDANE's rule for hybrid sterility as well as for inviability? To answer to these questions, we must briefly review the dominance theory.

The dominance theory: MULLER (1940, 1942) presented an intuitive explanation of the connection between HALDANE's rule and the recessivity of incompatibilities. Our dominance theory translates his intuition into algebra and, like ORR's (1993a) original analysis, confirms that dominance has a profound effect on the fitness of hybrid males relative to hybrid females. In particular, we show that HALDANE's rule results whenever the alleles causing postzygotic isolation act as partial recessives [$d < 1/2$; see Equation 6 of TURELLI and ORR (1995) for the definition of this dominance parameter]. The reason is simple. Assume, for concreteness, that males are the heterogametic sex. Hybrid males suffer the full hemizygous brunt of all *X*-linked incompatibilities—whether dominant or recessive—while females suffer only the "masked" heterozygous effects of these incompatibilities. Females, however, suffer from *twice* as many hybrid incompatibilities involving the *X* as males (because females carry twice as many *X*s). These two forces balance in our model when $d = 1/2$. But hybrid males are, on average, worse off than females when $d < 1/2$ and HALDANE's rule results. This theory assumes only that hybrid fitness is a decreasing function of the cumulative additive effects of incompatibilities (*i.e.*, the exact shape of the function mapping incompatibilities onto fitness is not important) and that incompatibilities affecting males *vs.* females appear at the same rate (see below).

The dominance theory says nothing about *why* the alleles causing hybrid problems act as partial recessives. It merely says that *if* they are recessive, HALDANE's rule will follow. We have, however, speculated about the cause of this recessivity. ORR (1993a) suggested that the alleles causing hybrid problems may act as loss-of-function mutations when placed on a hybrid genetic background: we have no guarantee that gene products will function efficiently when placed in a milieu of "foreign" substrates (indeed it would be very surprising if all products did). Loss of fitness in hybrids might, therefore, result from loss of gene function. As WRIGHT (1934) and KACSER and BURNS (1981) emphasized, alleles showing such loss of function tend to act recessively.

This loss-of-function mechanism is obviously specula-

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tive. But the important point is that this speculation about mechanism can be distinguished from the dominance theory *per se*: the dominance theory holds *no matter why* "speciation genes" act as partial recessives.

Dominance and the "composite" theory of sterility: No recent writer seems to doubt that dominance alone can account for HALDANE's rule for hybrid inviability. But the situation with hybrid sterility is more complex. The reason is that, while the alleles causing lethality typically kill both sexes, the alleles causing sterility typically sterilize one sex only. Thus, we have no assurance that equal numbers of alleles lower the fertility of hybrid males *vs.* females in any hybridization.

Indeed, WU and DAVIS (1993) have speculated that sexual selection and/or the greater inherent sensitivity of spermatogenesis cause a faster accumulation of hybrid male than female steriles. If so, this differential accumulation could help cause HALDANE's rule for sterility. It is important to notice, though, that neither sexual selection nor the "spermatogenesis is special" hypothesis can explain HALDANE's rule for sterility in birds or Lepidoptera. In these taxa—which nicely obey HALDANE's rule—hybrid *females* are preferentially sterile, and any sexual selection or greater sensitivity of spermatogenesis would work *against* HALDANE's rule. Hence, the WU and DAVIS (1993) hypotheses cannot explain HALDANE's rule for sterility in two major animal taxa. But in taxa where males are heterogametic (*e.g.*, Drosophila and mammals), forces like sexual selection may well contribute to HALDANE's rule for sterility. In these taxa, HALDANE's rule might be a "composite" phenomenon: several factors may differentially lower the fitness of heterogametic hybrids.

Our claim, however, is that factors like sexual selection get *added on top of* the underlying recessivity of speciation genes. We believe this recessivity is general in two different ways. First, we suspect that both hybrid lethals *and* steriles act as partial recessives. We see no biochemical reason why the mode of gene action should qualitatively differ between these two phenotypes. Indeed, both lethals and steriles are typically recessive *within* species. [Recessive female steriles are about 50–75 times more common than dominant female steriles in *D. melanogaster* (ASHBURNER 1989, pp. 434–436). Although the male data are more anecdotal, the majority of male steriles—barring chromosomal *T(X;A)* sterility—appear to be recessive (ASHBURNER 1989, pp. 438–440; LINDSLEY and TOKUYASU 1980).] If the alleles causing hybrid inviability act as partial recessives, and the evidence overwhelmingly suggests they do (ORR 1993b), it seems reasonable to expect that the alleles causing sterility also act as recessives. Second, we posit that this recessivity characterizes speciation genes in *all* animal taxa. Our conjecture, then, is that recessivity contributes to HALDANE's rule for both inviability and sterility in all animal taxa.

The mathematics of HALDANE's rule become more complex when additional forces—like the differential accumulation of male *vs.* female steriles or the faster evolution of *X*-linked genes—act on top of this underlying recessivity. We considered these complications in APPENDIX B of TURELLI and ORR (1995), where we presented a formal "composite theory" of HALDANE's rule. We showed that HALDANE's rule holds on average whenever the dominance parameter, d, satisfies

$$d < \frac{\tau p_x}{2[1 - \tau(1 - p_x)]}, \qquad (1)$$

where τ measures the relative cumulative effects of incompatibilities affecting hybrid male *vs.* female fertility and p_x is the fraction of incompatibilities involving *X*-linked genes. If hybrid male and female steriles evolve at the same rate, $\tau = 1$ and inequality (1) reduces to $d < 1/2$, just as with viability. If, however, male steriles accumulate faster than female, $\tau > 1$ and HALDANE's rule can result even when $d \geq 1/2$.

To show this, we plot inequality (1) in Figure 1 for various values of p_x. Values of d below each curve yield HALDANE's rule, while values above each curve result in most hybridizations violating HALDANE's rule. We consider three different values of p_x. The value $p_x = 0.36$ may be reasonable for Drosophila: since about 20% of loci in *D. melanogaster* are *X*-linked, $1 - (4/5)^2 \approx 0.36$ of all incompatibilities should involve the *X*, assuming incompatibilities involve random pairs of loci (ORR 1995). If, on the other hand, incompatibilities involve sets of three genes, an analogous calculation gives $p_x \approx 0.5$. In contrast, a value of $p_x \approx 0.1$ may be more reason-

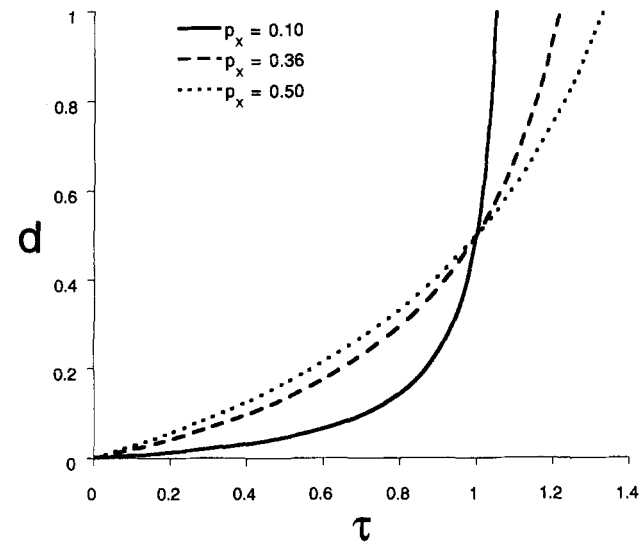

FIGURE 1.—A composite theory of HALDANE's rule. The parameter τ measures the relative cumulative effects of incompatibilities affecting hybrid male *vs.* female fertility; if $\tau > 1$, there is an evolutionary bias in favor of male steriles. Values of d below the lines produce HALDANE's rule; values above tend to produce exceptions. The different curves correspond to different values of p_x, the fraction of incompatibilities that involve *X*-linked loci.

able for taxa having smaller sex chromosomes [but may be too small if incompatibilities often involve many loci (MULLER 1942, CABOT *et al.* 1994)]. Figure 1 shows that if there are significantly more male than female steriles, HALDANE's rule arises with virtually any degree of dominance. Conversely, when $\tau < 1$, greater recessivity is required for HALDANE's rule as p_x decreases. [Figure 1 also suggests that an excess of male steriles explains the fertility of "unbalanced females" (see COYNE and ORR 1989) better than the argument presented in TURELLI and ORR. Similarly, our previous estimate of dominance based on the time lag between male *vs.* female inviability/sterility can be improved (and increased) by allowing for sex differences in the accumulation of steriles.]

Several important points about the composite theory are not immediately obvious from Figure 1. First, although recessivity may not be required for HALDANE's rule when male steriles accumulate faster than female, it does *not* follow that the steriles involved are not recessive. Indeed we predict that they typically are. Nor does it follow that HALDANE's rule is caused by one factor and not the other. It is entirely possible that *either* the excess of male over female steriles *or* their recessivity is sufficient to cause HALDANE's rule when acting alone. [Indeed, Equation 1 shows that if speciation genes are sufficiently recessive ($d < {}^1/_2$), an excess of male steriles is not required to obtain HALDANE's rule.] If each of several forces is sufficient (when taken alone) to give HALDANE's rule, it is meaningless to ascribe the cause of HALDANE's rule to any particular one.

Second, even in taxa where male steriles may be more common than female (*e.g.,* Drosophila), there is circumstantial evidence for the recessivity of hybrid sterility genes. In particular, the disproportionate effect of the *X* chromosome on hybrid sterility (COYNE and ORR 1989) cannot be explained by faster accumulation of male steriles. This well-known pattern suggests that the genes involved act as partial recessives in hybrids. This conclusion is not certain, however, as the large *X*-effect could reflect the faster evolution of *X*-linked loci, as CHARLESWORTH *et al.* (1987) suggested. Direct tests of the dominance of hybrid sterility alleles in Drosophila are needed.

Third, as noted above, any excess of male over female steriles makes it more difficult to obtain HALDANE's rule in taxa where females are heterogametic. The fact that birds and Lepidoptera obey HALDANE's rule for sterility implies, then, that the genes involved are recessive enough to *overcome* any such effect. Indeed these taxa afford a unique opportunity to calculate the maximum dominance consistent with HALDANE's rule. If, for instance, only 10% of hybrid incompatibilities involve the *X* (which may be plausible for birds and butterflies) and hybrid male steriles are five times more common than female steriles [as suggested by recent work in Drosophila (TRUE *et al.* 1996; H. HOLLOCHER, personal communication)], HALDANE's rule results only if $d \leq 0.01$ (Figure 1). (With $p_x \geq 0.2$, the condition becomes $d \leq 0.02$.) If d were much greater than this, the excess of male steriles would overwhelm the effects of recessivity, and birds and butterflies would not obey HALDANE's rule for sterility. It is worth noting that extreme recessivity is consistent with what is known about the dominance of lethals and steriles *within* species: data from Drosophila suggest that the typical lethal is almost, but not completely, recessive (SIMMONS and CROW 1977). (As noted above, the data for sterility are far less quantitative, but most steriles appear to act recessively.) It is also worth noting that, if incompatibilities often involve several loci (MULLER 1942; CABOT *et al.* 1994), larger values of p_x will result and, consequently, larger values of d will be consistent with HALDANE's rule.

In sum, while it is entirely possible that HALDANE's rule is a composite phenomenon in some taxa, we conjecture that dominance is an invariant ingredient in the mix of factors contributing to HALDANE's rule. If it is not, then some as yet unknown cause of HALDANE's rule must act in birds and butterflies.

Conclusions: We hypothesize that the alleles causing hybrid sterility and inviability act as partial recessives—and thus give rise to HALDANE's rule—in all animal taxa. While additional forces like sexual selection may well contribute to HALDANE's rule in some taxa, they work against HALDANE's rule in other taxa. The validity of the dominance theory is independent of the mechanistic cause of hybrid recessivity.

We thank N. H. BARTON, D. J. BEGUN, C. C. LAURIE and especially J. A. COYNE for helpful comments and discussion, and H. HOLLOCHER for showing us her unpublished data. This research was supported in part by National Institutes of Health grant GM-51932, the David and Lucile Packard Foundation, and National Science Foundation grant BSR 91-19463.

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Communicating editor: M. LYNCH