Letters to the Editor

Meiotic Drive and Unisexual Hybrid Sterility: A Comment

HURST and POMIANKOWSKI (1991) recently proposed that Haldane's rule (the tendency for the heterogametic sex to suffer disproportionately from loss of fitness in interspecies hybrids) may be a result of the fixation of meiotic drive elements on the sex chromosomes. They suggest (p. 848) that "novel drive systems will evolve more quickly on the sex chromosomes of the heterogametic sex." This is said to lead to the fixation of different suppressors of driving *X* and *Y* chromosomes in different species, leading to an incompatibility of heterospecific *X* and *Y* chromosomes in heterogametic hybrids due to mutual drive of *X* and *Y* chromosomes. In addition, they advance several objections to the model proposed by CHARLESWORTH, COYNE and BARTON (1987) and COYNE and ORR (1989) to explain Haldane's rule and the prominent role of the sex chromosomes in the control of hybrid fitness loss. In this note, we wish to comment on some aspects of the factual and theoretical evidence that they cite in support of their theory, and to respond to their comments on our own work.

FRANK (1991a,b) has proposed a theory similar to that of HURST and POMIANKOWSKI, which has been discussed elsewhere (COYNE, CHARLESWORTH and ORR 1991; JOHNSON and WU 1992). Many of these points made in reply to FRANK apply to HURST and POMIANKOWSKI's work, and we shall not repeat them here, except to note that there are several cases of Haldane's rule in which the *Y* chromosome has no effect on hybrid sterility (COYNE, CHARLESWORTH and ORR 1991). This is difficult to account for by their model. In addition, and in common with FRANK, their model has considerable difficulty in explaining cases of hybrid inviability as a result of meiotic drive, except by invoking *ad hoc* assumptions about the involvement of transposable elements in the causation of meiotic drive, which lack empirical support. Indeed, there is evidence against an important role for transposable elements in causing reproductive isolation in Drosophila (COYNE 1986).

HURST and POMIANKOWSKI (p. 854) claimed that the *Y* is involved in causing male inviability in hybrids between *Drosophila melanogaster* and *Drosophila sechellia*, because of the inviability of *XY* males and the viability of *XO* males in the progeny of crosses between *melanogaster* females and *sechellia* males HUTTER 1990). This experiment does not, however, provide definitive evidence for a role of the *Y* chromosome in causing inviability. The viable and inviable males in these crosses differ with respect to the origin of the *X* chromosome as well as the *Y*, since the *XO* males are produced by fertilization of a nullo-*X* egg by a sperm containing a *sechellia X*. Evidence reviewed by HUTTER, ROOTE and ASHBURNER (1990) shows clearly that there is no role of the *Y* chromosome in the control of hybrid inviability in crosses between *D. melanogaster* and *D. simulans*.

There is thus no evidence to support a key prediction of their model–a universal involvement of the *Y* chromosome in hybridizations obeying HALDANE's rule. There is also no evidence for naturally occurring *Y*-linked drive in Drosophila. The example that HURST and POMIANKOWSKI cite in their Table 1 (*Drosophila affinis*) does not, in fact, involve *Y*-linked drive. As shown by VOELKER (1972), male-biased progenies in this species are probably the result of the production of a high frequency of nullo-*X* sperm by a sex-ratio *X* chromosome in *XO* males (the sex-ratio *X* drives the *Y* in *XY* males). A recent genetic analysis of hybrids between *D. simulans* and *D. sechellia*, in which male F_1 hybrids are sterile, has failed to detect any evidence for meiotic drive of the sex chromosomes (JOHNSON and WU 1992). Data on three other Drosophila hybridizations also fail to show evidence for meiotic drive of the sex chromosomes (COYNE and ORR 1992). The lack of evidence for *Y* chromosome effects on both meiotic drive and hybrid inviability in Drosophila is not surprising, in view of the small number of genes that map to this chromosome (ASHBURNER 1989, Chap. 20).

HURST and POMIANKOWSKI's most important theoretical result concerns the condition for the invasion of a population by an *X*-linked distorter allele that causes destruction of the *Y* chromosome in heterogametic individuals (their Equation 4). Their derivation is based on the assumption that the state of the population can be described by an average frequency of the driving *X* allele, weighting the frequency in females by 2/3 and the frequency in males by 1/3. But this procedure is exact only for a neutral *X*-linked allele, and so is likely to introduce significant deviations from the exact results when drive is strong.

The following analysis, using standard techniques for determining invasion conditions, can be used to obtain exact results. For convenience, we shall assume male heterogamety. Following HURST and POMIANKOWSKI, consider the case when the population of *X* chromosomes is initially fixed for a nondistorting allele (d) at the distorter locus in a two-locus distorter/responder system (CHARLESWORTH and

HARTL 1978; WU and HAMMER 1990). The population is segregating for a pair of selectively neutral alleles (responder-sensitive, *i*, and responder-insensitive, *I*) at the responder locus, with a frequency of γ of *I*. A mutation to the distorter allele *D* is assumed to arise in a gamete carrying the insensitive allele at the responder locus *I*. Males carrying the *DI X* chromosome produce a fraction *K* of *X* chromosomes in their gametes, and suffer fitness loss *U*. The frequency of recombination between the two loci in females is *r*. Let the frequency of *DI X* chromosomes be *x* in female gametes and *y* in male gametes. These frequencies are assumed to be so small that second-order terms can be neglected.

It follows that the frequencies of female zygotes of genotype *DI/di* and *DI/dI* are $(1 - \gamma)(x + y)$ and $\gamma(x + y)$ respectively, and the frequency of males of genotype *D I* is *x*. Using the above assumptions about recombination and drive, we obtain the following recurrence relations:

$$x' = \tfrac{1}{2}(1 - [1 - \gamma]r)(x + y) \qquad (1a)$$

$$y' = 2K(1 - U)x. \qquad (1b)$$

The characteristic equation is

$$f(\lambda) = \lambda^2 - \tfrac{1}{2}\lambda(1 - [1 - \gamma]r) - K(1 - U)(1 - [1 - \gamma]r) = 0. \qquad (2)$$

It is easily seen that this equation has real roots, and that its derivative at $\lambda = 1$ is positive. A necessary and sufficient condition for instability of the initial equilibrium to the introduction of *D* is thus $f(1) < 0$, *i.e.*,

$$\frac{2K(1 - U) - 1}{(1 - \gamma)(1 + 2K[1 - U])} > r \qquad (3)$$

The corresponding formula derived from HURST and POMIANKOWSKI's Equation 4 is

$$\frac{2K(1 - U) - 1}{2(1 - \gamma)} > r. \qquad (4)$$

Equation 3 is a more stringent condition than (4), since a necessary condition for invasion is $2K(1 - U) > 1$.

It is of interest to compare Equation 3 with the condition for invasion by an autosomal distorter chromosome in a species with no male recombination, derived by CHARLESWORTH and HARTL (1978). Here, the evidence from the *D. melanogaster SD* system suggests that the insensitive allele at the responder locus must suffer a fitness disadvantage (CHARLESWORTH and HARTL 1978; WU, TRUE and JOHNSON 1989), and so it is reasonable to assume that the initial state of the population is such that $\gamma = 0$. The invasion condition is

$$2K(1 - U) - 1 > r \qquad (5)$$

where *K* is the frequency of *DI* chromosomes in the sperm produced by *DI/di* males. Comparing equations (3) and (5), we see that, assuming the same drive and fertility parameters for the autosomal and sex-linked cases, invasion by an *X*-linked distorter occurs for the same maximum value of *r* as in the autosomal case if and only if $(1 - \gamma)(1 + 2K[1 - U]) \leq 1$. A necessary condition is that $\gamma > 0.5$, *i.e.*, the insensitive allele must have achieved a frequency of more than 50% before invasion by the distorter, which is the condition derived from HURST and POMIANKOWSKI's Equation 4.

Under many circumstances it is thus more difficult for a distorter system to invade on the *X* chromosome than on the autosomes. The intuitive reason for this, noted by COYNE, CHARLESWORTH and ORR (1991), is that (with no crossing over in the heterogametic sex) an *X* chromosome spends two-thirds of its time in females, as opposed to one-half for an autosome. There is thus more opportunity for recombination to disrupt associations between distorting elements and other genes with which they interact. In contrast, HURST and POMIANKOWSKI (1991) and FRANK (1991a) emphasize the fact that an *X*-linked distorter allele can invade more easily than an equivalent autosomal allele when the insensitive allele at the responder locus is at a high frequency on the *X* chromosome (but not the *Y* chromosome). While this is true, there is, as already noted, evidence that such alleles may be deleterious. Thus there are reasons to doubt that they will be maintained in the absence of distorter alleles. Only more detailed genetic analysis of sex-ratio distorter systems can resolve this issue.

We now turn to HURST and POMIANKOWSKI's critique of our own model (CHARLESWORTH, COYNE and BARTON 1987; COYNE and ORR 1989). This model appeals to the expected faster rate of substitution of favorable partially recessive or underdominant alleles on the sex chromosomes compared with the autosomes, in order to explain both Haldane's rule and the large effect of the *X* chromosome often observed in cases of hybrid fitness loss. Their first point (p. 853) is that we "suggest no clear reason or possible mechanism why the faster accumulation of advantageous recessives on *X* chromosomes results in hybrid sterility, inviability or absence." Such a mechanism was in fact proposed by DOBZHANSKY (1937) and MULLER (1940) long ago. It simply postulates that alleles that are selected within a population may fail to interact favorably with alleles at other loci which have been independently selected in another, isolated population. There is now abundant evidence from species crosses that postzygotic isolation results from such epistatic interactions (COYNE 1992), starting with the classic work of DOBZHANSKY (1936). An explicit example of such a model of hybrid fitness loss was presented by CHARLESWORTH, COYNE and BARTON (1987, pp. 130–131).

HURST and POMIANKOWSKI also state that "the advantageous recessive theory fails to explain why there is no greater contribution of the *X* chromosome to morphological or behavioral differences between species." This question was discussed by CHARLESWORTH, COYNE and BARTON (1987, pp. 130, 135); we pointed out that these differences in the mode of genetic control of species differences be explained if the genes causing hybrid fitness have been "selected for as major genes, contributing the bulk of the genetic variance in the characters that they affect during the period of their spread and fixation." In contrast, many morphometric traits are likely to be controlled by approximately additive polygenic systems. Since the evolution of reproductive isolation requires strong epistatic interactions, the loci concerned may well be a nonrepresentative sub-set of those distinguishing the species. The deviations from additivity implied by the existence of these interactions between alleles at different loci are likely to require relatively large gene effects, which in turn may be associated with non-additive interactions between alleles at the same locus (KACSER and BURNS 1981). This additional assumption concerning the nature of the genes involved in postzygotic isolation is thus at least plausible.

Further evidence on the nature of the genetic control of species differences should help to answer these questions. In particular, we predict that any cases where a disproportionate effect of the *X* is found to underlie morphological differences between races or species will involve genes of relatively major phenotypic effect, and that the more recessive alleles at the *X*-linked loci concerned will be derived rather than ancestral. There is already some evidence from hybridizations in Lepidoptera for *X*-linked genes with large phenotypic effects (HAGEN and SCRIBER 1989).

HURST and POMIANKOWSKI's second point is that slightly deleterious alleles will accumulate faster on the autosomes and so "On the assumption that neutral or nearly neutral mutants are the major factor contributing to molecular evolution, we would expect that the autosomes will change more quickly than the *X*" (p. 853). This is in agreement with the conclusions of CHARLESWORTH, COYNE and BARTON (1987), who suggested that the well documented disproportionate involvement of the *X* in the genetic control of hybrid sterility implies that the genes concerned have been fixed by natural selection rather than genetic drift (p. 130). As pointed out above, it seems unlikely *a priori* that genes with very slight fitness effects could be important in the evolution of hybrid fitness loss, and there are certainly no grounds for assuming that the gene differences concerned are a random sample of the changes occurring in molecular evolution.

This is also relevant to their third point, where they invoke evidence that mutation rates in mammals are higher in males than females (MIYATA *et al.* 1987) and suggest that "if genetic distance is the cause of hybrid sterility then we would predict that the loci for sterility should predominantly map to the autosomes" (p. 854). We note, however, that a higher mutation rate in males than females means that the model of CHARLESWORTH, COYNE and BARTON (1987) requires favorable genes to be more completely recessive in order to produce a given excess rate of evolution on the *X*, than for the case when mutation rates are the same in the two sexes. Although there is increasingly good evidence that male mutation rates at some loci in mammals are considerably higher than in females (DRYA *et al.* 1989), this does not appear to be the case in Drosophila (WOODRUFF, SLATKO and THOMPSON 1983, Table 1), from which much of the evidence for large *X* chromosome effects in the control of reproductive isolation is obtained. Moreover, in species with female heterogamety, such a sex difference in mutation rates would be favorable to our model.

In summary, there seem to be several major empirical and theoretical difficulties with the theory that the phenomena associated with unisexual hybrid fitness loss, such as Haldane's rule and large *X* effects, are the product of meiotic drive. We do not mean to imply that our own theory is conclusively established, but we do wish to correct the impression that potentially fatal difficulties to it have been raised by HURST and POMIANKOWSKI. It may turn out, of course, that yet another theory will be proposed and validated.

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