Genomic Conflicts Underlying Haldane's Rule

Neither the genetic cause nor the evolution of unisexual hybrid sterility are well understood. Recently we (HURST and POMIANKOWSKI 1991a) suggested that sex ratio distorters might be involved in unisexual hybrid sterility and explain Haldane's rule, the finding that unisexual disruption occurs predominantly in the heterogametic sex (see also FRANK 1991). We discussed the importance of two broad categories of distorter: cytoplasmic sex ratio distorters and meiotic drive genes. We found strong theoretical and empirical support for the hypothesis that hybrid disruption could result from selfish genetic elements attempting to pervert the sex ratio. If this evidence is accepted then the issue is not whether but how widespread is the involvement of sex ratio distorters in unisexual hybrid sterility.

The evidence for the involvement of meiotic drive genes has proved to be controversial. CHARLESWORTH, COYNE and ORR (1992) claim to have discovered major theoretical and empirical reasons why Haldane's rule cannot in principle be explained by conflicts between sex chromosomes. They (a) challenge our conclusion that meiotic drive systems are more likely to evolve on sex chromosomes, (b) suggest that many cases of hybrid sterility are not compatible with a meiotic drive explanation and (c) reiterate their support for a model of Haldane's rule based on the faster evolution of recessive alleles on sex chromosomes. Although we agree with some of the points raised by CHARLESWORTH, COYNE and ORR, in general their challenge is unconvincing and mistaken. It is based on an incomplete theoretical analysis and misunderstandings about how meiotic drive genes might cause sterility. We remain confident that the evolution of sex ratio distorters within species, and selfish genetic elements in general, can in principle explain cases of hybrid sterility. We discuss numerous examples where meiotic drive appears to be involved in sterility.

Drive on *X*, *Y* and autosomes: Genes causing Haldane's rule hybrid sterility, (*i.e.*, heterogametic sex only) are often, though not exclusively linked to the *X* (COYNE and ORR 1989). The *X* chromosome has at least two unusual features that might explain this: first it is hemizygous in the heterogametic sex and second it does not cross over with the *Y*. Most hypotheses about Haldane's rule have linked the greater involvement of the *X* to its hemizygosity (CHARLESWORTH, COYNE and BARTON 1987; COYNE and ORR 1989). We wondered whether the absence of crossing over might give the *X* unusual properties that could potentially explain Haldane's rule. Are there genes that not only evolve faster on the *X* because of the lack of crossing over but also are involved in hybrid sterility? We argued that meiotic drivers might be such genes. The argument has two facets. First, one can ask which chromosomes are more likely to evolve meiotic drive and second, what connections there are between drive and sterility (see below)?

WU and HAMMER (1990), FRANK (1991) and HURST and POMIANKOWSKI (1991a) argued that sex chromosome drive might be more prevalent than autosomal drive because of the lack of recombination between *X* and *Y*. The logic is relatively simple. Drive chromosomes must be insensitive to their own action, whilst the chromosomes they exploit must be insensitive to the driver's action. As *X* and *Y* never recombine, the *X* can be at fixation for insensitivity while all *Y* chromosomes remain sensitive to drive. An *X* linked driver is thus more likely to invade the higher the frequency of insensitivity (and the same for a *Y* linked driver and the frequency of insensitivity on the *Y*).

The reverse is true of autosomes. For invasion of autosomal drive, the insensitivity allele must be rare. If insensitivity is common then most chromosomes will be immune to the action of the driver. The most likely reason for insensitivity to be rare is that it is mildly deleterious (WU, TRUE and JOHNSTON 1989). Insensitive sites favoured by selection are unsuitable, because if insensitivity is at all common most chromosomes will be immune to drive. This restricts the set of imaginable insensitive mutations that permit autosomal drive to invade to those kept at low frequency. For *X* and *Y* drive any frequency of insensitivity will do and higher frequencies are better.

The need for rarity puts on a further constraint on autosomal drive. A newly arising driver will only have a chance to invade if it occurs on a chromosome carrying an insensitive target allele. A driver linked to a sensitive allele will reduce its own transmission rate as much as that of its homolog and in most cases will be quickly eliminated. But if insensitivity is rare the probability an autosomal driver arises linked to insensitivity is low. It is far more likely that the driver is initially linked to sensitivity and is lost.

We put this argument on a surer footing by modeling the invasion of drivers. Surprisingly, CHARLESWORTH, COYNE and ORR's rederivation of our results (using slightly different assumptions) comes to the opposite conclusion, that under many conditions drive is more likely to invade on autosomes than on the sex chromosomes. However, this discrepancy is due to the incomplete nature of CHARLESWORTH, COYNE and ORR's analysis.

To see this consider the invasion of a meiotic drive gene linked to an insensitive allele on either *X*, *Y* or autosome (HURST and POMIANKOWSKI 1991a). In males heterozygous for drive (*DI/di*) a fraction *K* gametes are *DI* (*K* = 0.5 no drive, *K* = 1.0 complete drive). Let the frequency of insensitivity by γ, so a fraction $1-\gamma$ chromosomes are susceptible to drive (*di*), the rest being insensitive to drive (*dI*). In males heterozygotes for drive and insensitivity (*DI/dI*) the drive chromosome has no segregation advantage. For simplicity we assume that drive occurs only in males and recombination only in females. The frequency of recombination between the drive and sensitivity loci in females is *r*. Males with the drive chromosome suffer a fitness loss *U* due to the deleterious effects of drive on fertility. Using these assumptions invasion of a drive allele, linked to *X*, *Y* or autosome, occurs if the fitness loss caused by the drive chromosome satisfies

$$U<\frac{2K-1-r(1-\gamma)(1+2K)}{2K(1-r+r\gamma)}, \quad X\text{chromosome};$$

$$U<\frac{2K-1}{2K}, \quad Y\text{chromosome};$$

$$U<\frac{(1-\gamma)(2K-1-r)}{2K(1-\gamma)+\gamma}, \quad \text{autosome.} \qquad (1)$$

For the *X* chromosome we follow CHARLESWORTH, COYNE and ORR's (1992) derivation, though qualitatively the same results hold for our own equation.

First we compare how the cost of drive (*U*) changes with the frequency of insensitivity (γ) for *X* and autosome drive (Figure 1A). In general the condition for invasion (larger maximum *U*) is more lenient for *X* drivers except if the rate of recombination is high or if the frequency of insensitivity is low. The case of a high recombination rate is probably not relevant as tight linkage appears to be common for autosomal drive (WU and HAMMER 1990; LYTTLE 1991). So only if insensitivity is at low frequency will conditions be marginally more favourable to autosomal drive.

But this is only a partial analysis. For invasion the driver must be linked to an insensitive allele, otherwise it attacks its own chromosome. When insensitivity is rare the probability of this coupling is low. We can calibrate this effect by taking the probability that a new drive allele arises linked to an insensitive allele (γ) and multiplying it by the probability that the value of *U* satisfies Equation 1. It is assumed that the distribution of *U* values is uniform and independent of linkage, and novel drive alleles which arise linked to sensitive alleles are eliminated. We can now plot the probability of invasion given a particular frequency of insensitivity (Figure 1B). This shows that the chances of *X* linked drive invasion are generally better. The same is true comparing *Y* and autosome linked drive (Figure 2B). The theoretical evidence supports our original conclusion that the conditions for invasion of sex linked drive are much more permissive than for autosomal drive. CHARLESWORTH, COYNE and ORR's different view stems from not considering the frequency of insensitivity or how drivers come to be linked to insensitivity.

CHARLESWORTH, COYNE and ORR's assumption that the initial state of the population is always $\gamma = 0$ (*i.e.*, the insensitivity allele is extremely rare) follows from the finding that insensitivity in *SD* is deleterious (WU, TRUE and JOHNSTON 1989). This deduction must be rejected. *SD* is a case of autosomal drive. If insensitivity had been advantageous it would have spread to fixation and thus prevented drive invasion. This tells us that autosome drive is restricted to insensitive sites under negative selection. Generalizing from autosome insensitive sites to those on the *X* or *Y* is not valid. There is no requirement for negative selection or low frequency insensitive sites on the sex chromosomes (see Figures 1 and 2). There is no reason for the assumption that $\gamma = 0$ on sex chromosomes. Far from undermining our position, the finding of a cost to insensitivity on an autosomal driver reaffirms our view that the conditions for drive on autosomes are restrictive.

If for some reason insensitive sites on the *X* (or *Y*) are always held at low frequency then we would expect autosomal drive to be more or less as frequent as sex chromosome drive. However, for this point to be of any relevance, an explanation is needed for why *X* linked insensitivity only exists at low frequency. None has been given. In contrast, it is quite easy to find reasons why *X* chromosomes might be at fixation for insensitivity while the *Y* is fixed for sensitivity. Given the lack of crossing over, differentiation between *X* and *Y* is inevitable. Structural differentiation between *X* and *Y* might predispose them to drive or be driven against. The *Y* for instance is highly heterochromatic. If interference with heterochromatin packing is a means to drive (WU and HAMMER 1990; HURST 1992) then a large fraction of the *Y* might be vulnerable to drivers. If these structural aspects are required for other reasons (which they probably are) then insensitivity on the *X* will be advantageous and at fixation while sensitivity will be advantageous and at fixation on the *Y*. Clearly in cases of *X* against *O* drive (see WHITE 1973; GUNNARSSON and ANDERSSON 1992), the *O* is by definition at "fixation" for sensitivity. How could it be otherwise?

A reason why our calculations may be inaccurate is the assumption that drive chromosomes impose a fitness cost. Reduction in the fertility of individuals heterozygous for drive is likely because of the reduction in the number of functional sperm (WU 1983; BIRKHEAD and MØLLER 1992) and the energetic or other requirements of drivers. We assumed that these costs apply equally to couplings with wildtype (*DI/di*) and insensitive (*DI/dI*) chromosomes (HURST and

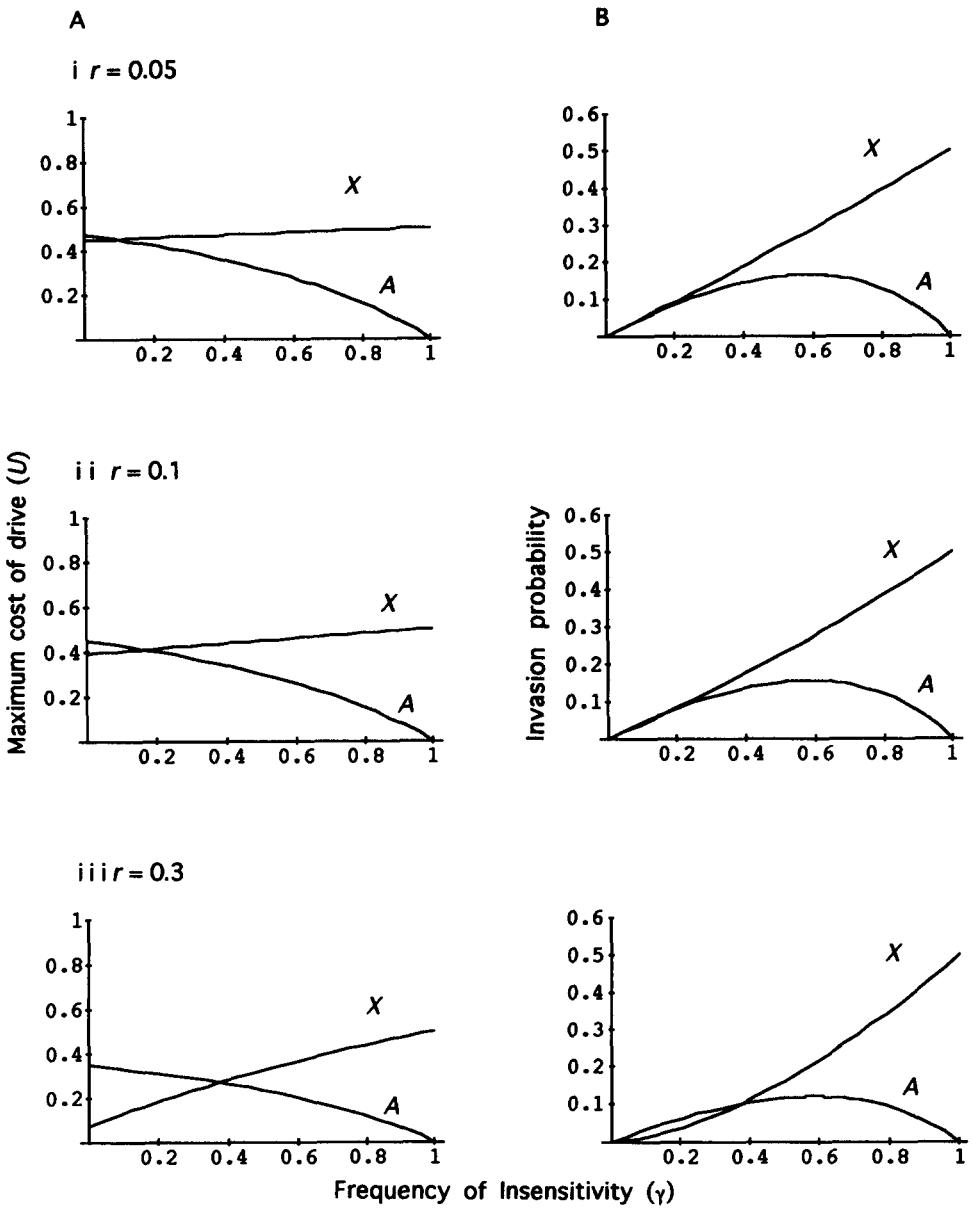

FIGURE 1.—(A) Comparison of the maximum cost of drive (U) for invasion of a drive element linked to the X chromosome (curve labeled X) or an autosome (curve labeled A) as functions of the frequency of insensitivity (γ). It is assumed that there is complete drive ($K = 1$), that is drive heterozygotes only produce mature gametes that contain the drive chromosome. Similar relationships hold for lower values of K, though with reduced values of maximum U. Three values of recombination are shown (i) $r = 0.05$, (ii) $r = 0.1$ and (iii) $r = 0.3$. (B) Invasion probability of a drive element linked to the X or an autosome as functions of the frequency of insensitivity (γ).

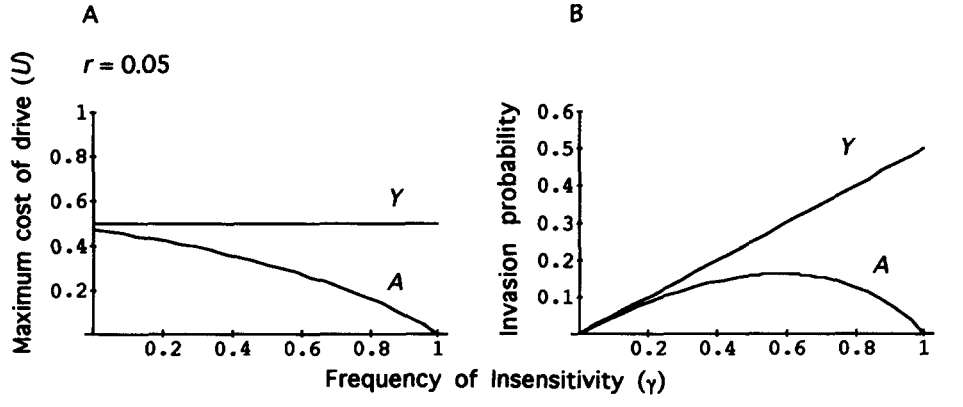

FIGURE 2.—Comparison of the (A) maximum cost of drive (U) and (B) invasion probability of a drive element inked to the Y chromosome (curve labeled Y) or an autosome (curve labeled A). These are shown as functions of the frequency of insensitivity (γ). $K = 1$ and $r = 0.05$.

POMIANKOWSKI 1991a), but this is an oversimplification. In DI/dI individuals drive is suppressed and the number of functional sperm is not diminished, reducing the cost of drive. Let the fitness of DI/dI individuals be reduced by cU ($0 < c < 1$). Now the condition for invasion of autosome linked drive is,

$$U < \frac{(1 - \gamma)(2K - 1 - r)}{2K(1 - \gamma) + c\gamma}. \quad (2)$$

If $c < 1$ there is weaker frequency dependent selection against autosome linked drivers (Figure 3A). As $c \rightarrow$

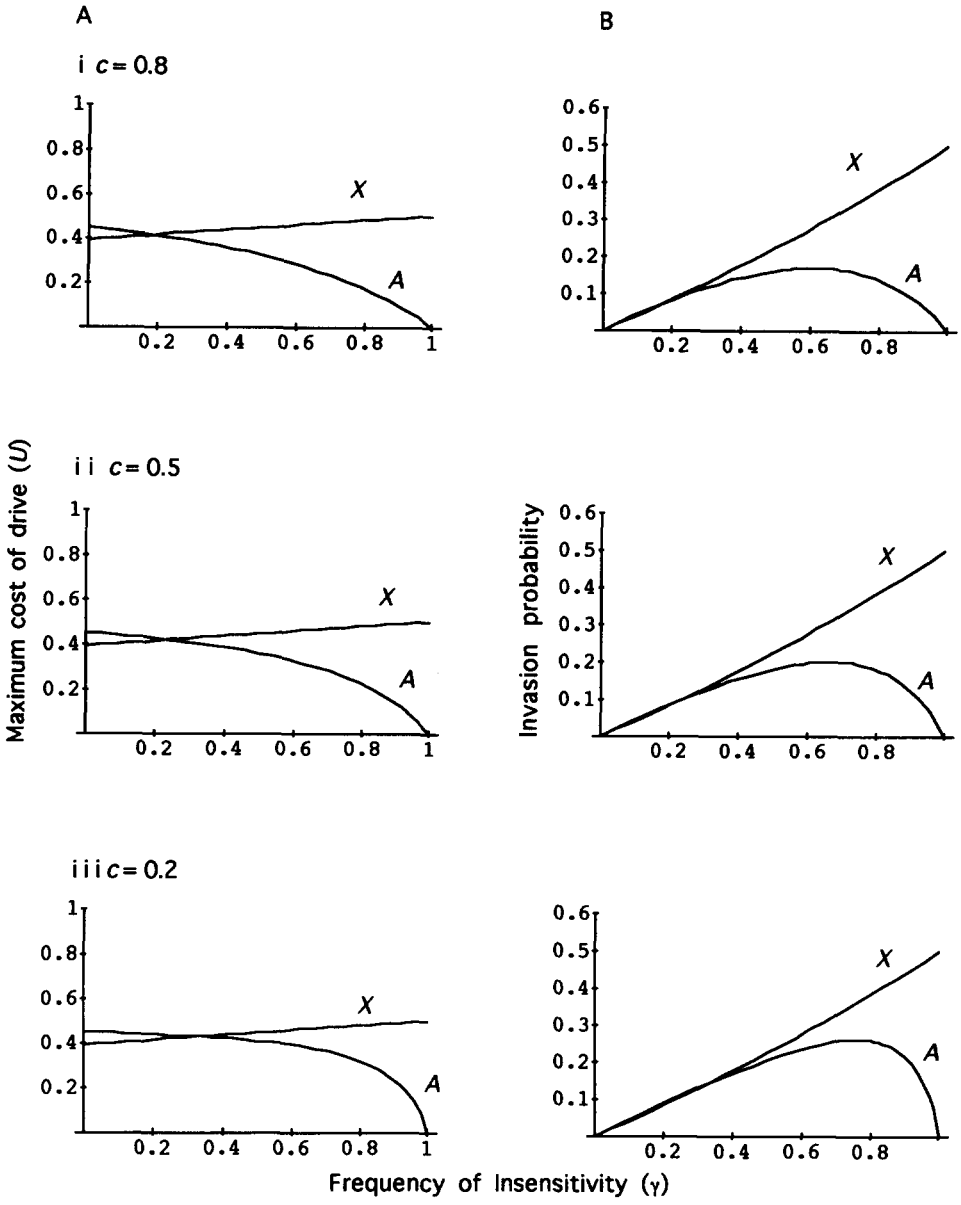

FIGURE 3.—Rederivation of Figure 1 when the fitness of *DI/dI* heterozygotes is $1 - cU$. (A) maximum cost of drive (U) and (B) invasion probability of a drive element linked to the X chromosome (curve labeled X) or an autosome (curve labeled A). This is shown for three values (i) c = 0.8, (ii) c = 0.5 and (iii) c = 0.2. K = 1 and r = 0.1.

0 this effect becomes more marked and the more permissive condition for X-linked drive is apparent only at high frequencies of insensitivity (Figure 3B). Even though this makes autosome drive easier to establish the same asymmetry remains: if insensitivity is rare (negatively selected) it is highly unlikely that a novel drive mutation is linked to an insensitive site, but if insensitivity is common (positively selected) most chromosomes are immune to drive. These limitations on autosome drive are likely to make it less common than drive located on the sex chromosomes.

Drive and sterility: There is abundant evidence that meiotic drive and sterility are causally related phenomena. Many examples can be given which fall into two broad model classes. Both connections between drive and sterility assume that coevolutionary turnover of drivers and their modifiers (suppressors and enhancers) causes differentiation between subpopulations. The first class of models involve drivers that are directly responsible for causing sterility. Drivers may only rarely cause transmission distortion in their own species either because they have gone to fixation or are normally suppressed (WU and HAMMER 1990). But in a hybrid, drivers might be released from suppression because of the lack of coevolved control mechanisms. If paternal and maternal chromosomes attempt to drive this could result in mutual destruction and sterility.

This model is empirically supported in several cases. In Neurospora fungi, several spore-killer meiotic drive systems (*Sk-2*, *Sk-3*, and *Sk-4*) achieve a transmission advantage in heterozygotes by eliminating ascospores that do not contain the spore-killer gene. Crosses between *Sk-2* and *Sk-3* strains can cause mutual drive and all ascospores abort (TURNER and PERKINS 1991; RAJU and PERKINS 1991). A similar de-

struction of all meiotic products due to mutual destruction has been observed in Podospora (TURNER and PERKINS 1991). Hybrids between *Oryza sativia* and *Oryza glaberrina* rice strains are male sterile. The three sterility genes involved (two in *O. sativia*, one in *O. glaberrina*) all cause meiotic drive when heterozygous on their normal genetic background (SANO 1990). The mechanism of sterility has not yet been shown to be due to mutual destruction by opposing drivers but the observations are consistent with such an interpretation.

Alternatively, drivers unleashed in the hybrid may have inappropriate action and result in general gametic breakdown rather than drive. One cause of this is the arms race between drivers, their targets and modifiers. Consider that a substance is necessary for (or lethal to) normal gamete maturation and that substance is preferentially sequestered (or preferentially deactivated) by the drive containing gamete. Modifiers defending the wildtype chromosome that heightened its affinity for the substance (or allow deactivation) will be positively selected. In turn this will lead to concomitant modifications to the drive chromosome. Hybridization with species that lack the drive system or have developed it to a different extent will result in ill-adapted responses to drive that cause sterility.

Such an interpretation may underlie the evolution of *Stellate*, one of the causes of sterility of *XO* males in *Drosophila melanogaster* (LIVAK, 1984, 1990; HURST 1992). *Stellate* is an *X*-linked gene which is suppressed in *XY* males by a *Y*-linked gene *Su(Ste)*. In the absence of *Su(Ste)*, in *XO* males, *Stellate* causes sterility. Both these loci consist of multiple copies of repeated sequence. It has been postulated that *Stellate* is a relict driver that coevolved in an arms race with *Su(Ste)*, its *Y*-linked suppressor (HURST 1992). We predict that in a hybrid context it is likely that *Stellate* will behave as it does in *XO* males and cause male sterility. Several lines of evidence support this view. In the complete absence of suppression in *XO* males, the effect of *Stellate* is too "strong" and the result is sterility. However, when *Stellate* has a low copy number on the *X* (and hence "weak") and the *Y* is deficient for *Su(Ste)*, as predicted not only are the organisms fertile but reciprocal meiotic products are not recovered with equal frequency, which LINDSEY and ZIMM (1992) describe as meiotic drive. The hypothesis is also supported from the preliminary confirmation of the prediction that the suppressor *Su(Ste)* repeats evolved after the *X*-linked *Stellate* (BALAKIREVA *et al.* 1992).

The second hypothesis linking drive and sterility suggests that general mechanisms which detect and eliminate defective meiotic divisions can be elicited by inappropriate meiotic drive in hybrids and result in a complete breakdown of meiosis (HURST and POMIANKOWSKI 1991a,b; A. POMIANKOWSKI and L. D. HURST, in preparation). A variety of general mechanisms for the protection of meiosis have been proposed. For example, MIKLOS (1974) proposed that saturation of pairing sites is an essential requirement for regular post-meiotic maturation of gametes. His view has recently been confirmed in studies of mice with abnormal sex chromosome karyotypes (*e.g.*, *XYY*, $X^{Sxr}O$, *XXY*). These often fail to show proper pairing and some or all of the sex chromosomes remain as univalents during metaphase. The result is meiotic breakdown and sterility (BURGOYNE, SUTCLIFFE and MAHADEVAIAH 1992). In a similar vein MCKEE (1991) has suggested that pairing is required for the initiation of early transcriptional inactivation of the *X* chromosome in Drosophila. Significantly pairing, drive and sterility are related as demonstrated by the finding that deficiencies in the *X* heterochromatic region required for pairing (the *bobbed* locus) causes either meiotic drive or sterility depending on the constitution of the *Y* chromosome (MCKEE 1991). Pairing domains are also involved in *X* linked sterility in male mice (MATSUDA, MOENS and CHAPMAN 1992). Similarly pairing failure has been considered to be a cause of oocyte loss and sex chromosome segregation distortion in female *XO* mice (KAUFMAN 1972; BURGOYNE and BAKER 1984).

In the context of the hybrid, anything unusual in meiosis might trigger these protective devices and cause gamete abortion. This will result in sterility if all gametes are affected. If these general mechanisms are activated by the action of drivers in the hybrid, this will cause sterility. Because pairing homology is restricted between *X* and *Y* chromosomes and drivers are more likely, the sex chromosomes should receive the most intensive meiotic surveillance. Hence slight problems associated with *XY* meiosis are likely to give rise to sterility. It is also likely that autosomes will be subject to such surveillance but to a lesser degree.

Again there is evidence for these kind of processes. A coevolutionary arms race probably explains the hybrid male sterility of crosses between *Mus domesticus* and *Mus spretus*. Sterility maps close to the *Tcd-2* locus on both the *t* drive and wild-type *M. domesticus* chromosome *17*, but not to the wild-type chromosome in *M. spretus* which lacks this drive system (PILDER, HAMMER and SILVER 1991). This suggests that coevolution between drive and wild-type chromosomes in *M. domesticus* has rendered both incompatible with the complementary chromosome in *M. spretus*. This interpretation is consistent with LYON's (1992) finding that *t* drive alleles are hypomorphs with which the wild-type chromosome has coevolved.

Another Drosophila example is *SR*, an *X* linked driver found in Tunisian populations of *Drosophila subobscura*. *SR* occurs at a high and stable frequency

(~30%) and produces female biased sex ratios. Crosses between Tunisian males with the *SR* driver and female laboratory stocks derived from wild European populations of the same species also produce female biased sex ratios. However, when F_1 hybrid females are backcrossed on the European stock, F_2 male offspring carrying the *SR* chromosome are nearly always sterile (HAUTSCHTECK-JUNGEN 1990). Nondriving *X* chromosomes of Tunisian origin do not cause sterility. In this example, as in many of the examples discussed here, the gene causing sterility could be the driver itself, a modifier of drive or a tightly linked gene not involved in drive. If the latter is the case, as a preliminary analysis suggests (HAUTSCHTECK-JUNGEN 1990), this begs the question as to why a gene causing interspecific sterility happens to be linked to a meiotic driver. The precise association between drive and sterility will require further close mapping to be elucidated.

In a series of experiments TURNER (1992) crossed *Neurospora intermedia* Spore killer (*Sk*) strains with samples taken from various geographic regions. This resulted in drive when the tested populations were sensitive to *Sk*, whereas crosses between *Sk* strains were generally fully fertile. However, in crosses with strains from New Zealand and Mexico all spores were aborted even though these strains completely lack Spore killers. TURNER (1992) suggests this may be due to a general anti-drive mechanism that has evolved to prevent the invasion of Spore killers. JOHNSTON and WU (1992) have pointed to another interesting case where interference with drive results in sterility. The autosomal *msr* genes in *Drosophila pseudoobscura* cause nondisjunction and sterility exclusively in the presence of an *X* driver (COBBS, JEWELL and GORDON 1991; COBBS 1992). Perhaps *msr* genes are a general anti-drive system. Irrespective of whether this interpretation is correct, these examples again show that drive and sterility are related phenomena.

Another possible involvement of drive in unisexual sterility concerns autosomal drive. Like *X* and *Y* drive, autosomal drivers are typically active in only one sex. To the best of our knowledge in nearly all well understood cases this is the heterogametic sex (with two exceptions: AGULNIK, AGULNIK and RUVINSKY 1990; LÓPEZ-LÉON, CABRERO and CAMACHO 1992), though we are wary of generalizing from so few examples. If these autosomal drivers cause hybrid disruption then only one sex will be affected and these cases will contribute to Haldane's rule. We have already given an example of this. In *M. domestica* transmission ratio distortion by *t* alleles only occurs in males. As predicted, sterility in *M. spretus* hybrids maps to the *t* complex and is similarly restricted to the male.

One of the views stressed in our original paper (HURST and POMIANKOWSKI 1991a) was that heterogametic sex sterility might be due to mutual drive. This had the virtue of making a clear prediction of how sterility emerges in a hybrid: *X* drives against *Y* and *Y* against *X*. Following our paper, JOHNSON and WU (1992) checked whether this could explain male sterility in hybrids between *D. simulans* and *D. sechellia*, and rejected the hypothesis. We are happy to see the hypothesis of mutual drive tested and refuted. However, JOHNSON and WU's experiments do not rule out other possible relationships between drive and sterility.

CHARLESWORTH, COYNE and ORR's criticisms are all specific to the mutual drive hypothesis as well. They are indeed correct to state that this hypothesis requires *Y* chromosome involvement. However, the notion that all drive models necessarily predict that the *Y* chromosome is involved in hybridizations is simply false. This is a necessary prediction only of the mutual drive model and only pertinent to those organisms with sex chromosomes. CHARLESWORTH, COYNE and ORR do not discuss other ways that drive and sterility might be related nor do they consider the body of data (and ideas) indicating that there are links between sterility and drive.

As we stated previously, we do not claim that all instances of sterility are the result of genomic conflict caused by meiotic drive genes, just that some might be (HURST and POMIANKOWSKI 1991a). Other genomic conflict, between imprinted genes and between nuclear and cytoplasmic genes, have been proposed as explanations of unisexual hybrid sterility and Haldane's rule (JABLONKA and LAMB 1991, HURST and POMIANKOWSKI 1991a, 1992). Any demonstration that conflict is not important in a given case of hybrid sterility does not demonstrate that conflict is irrelevant to all instances of sterility. By equal measure any demonstration that conflict is important does not demonstrate that it always is or that there cannot be other causes of sterility. As MAYR (1988) has previously cautioned several kinds of genetic changes probably play a role in reproductive isolation. What remains to be determined is the relative importance of the various hypothesized factors.

Summary: The theory proposing that sex chromosome drive might be more common than autosomal drive is theoretically sound and is supported by available empirical evidence (WU and HAMMER 1990; FRANK 1991; HURST and POMIANKOWSKI 1991a). Several hypotheses have been proposed connecting drive with hybrid sterility. Not all of these predict an involvement of the *Y* chromosome. Thus the absence of *Y* effects in hybrid disruption is not strong evidence against a relationship between drive and sterility. Drive hypotheses in general receive strong support from the frequent finding of associations between drive and sterility.

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