Causes of Sex Ratio Bias May Account for Unisexual Sterility in Hybrids: A New Explanation of Haldane's Rule and Related Phenomena

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ABSTRACT

Unisexual hybrid disruption can be accounted for by interactions between sex ratio distorters which have diverged in the species of the hybrid cross. One class of unisexual hybrid disruption is described by Haldane's rule, namely that the sex which is absent, inviable or sterile is the heterogametic sex. This effect is mainly due to incompatibility between *X* and *Y* chromosomes. We propose that this incompatibility is due to a mutual imbalance between meiotic drive genes, which are more likely to evolve on sex chromosomes than autosomes. The incidences of taxa with sex chromosome drive closely matches those where Haldane's rule applies: Aves, Mammalia, Lepidoptera and Diptera. We predict that Haldane's rule is not universal but is correct for taxa with sex chromosome meiotic drive. A second class of hybrid disruption affects the male of the species regardless of which sex is heterogametic. Typically the genes responsible for this form of disruption are cytoplasmic. These instances are accounted for by the release from suppression of cytoplasmic sex ratio distorters when in a novel nuclear cytotype. Due to the exclusively maternal transmission of cytoplasm, cytoplasmic sex ratio distorters cause only female-biased sex ratios. This asymmetry explains why hybrid disruption is limited to the male.

IN crosses between different species the offspring sometimes show disturbed sex ratios, one sex being absent, rare or sterile. In many cases the missing or sterile sex is the heterogametic sex, a generalization known as Haldane's rule after its discoverer (HALDANE 1922). Examples of this relationship are found in both the common case of male heterogamety (*XY* or *XO*) and where the female is the heterogametic sex (*ZW*), as in birds and butterflies (DAVIDSON 1974; GRAY 1954, 1958; COYNE and ORR 1989). There are some well known exceptions to this rule (CROW 1942; PATTERSON and GRIFFEN 1944; WHITE 1973, p. 569; BOCK 1984). Genetic analysis by MITROFANOV and SIDOROVA (1980) and ORR (1987) of some *Drosophila* species has shown that heterogametic sterility in these species is mainly due to *X-Y* incompatibility, with lesser *X*-autosome or *Y*-autosome contributions to sterility. Genes on the *X* chromosome responsible for heterogametic sterility have been identified (COYNE and CHARLESWORTH 1986, 1989).

In other cases hybrid sterility does not appear to be linked to heterogamety. Though there is strong evidence for Haldane's rule taking species as independent events, there is no significant association of heterogamety and sterility when phylogeny is strictly controlled for (READ and NEE 1991). Furthermore, unisexual sterility also occurs in crosses between insect or plant species that lack sex chromosomes (this paper; FRANK 1989). This second class of hybrid disruption appears to affect only the males in a cross, regardless of heterogamety. Males alone are absent, inviable or sterile. The genes for this effect are typically cytoplasmic.

We make the suggestion that both of these phenomena can be accounted for by a loss of suppression of sex ratio distorters when in the novel nuclear cytotype of the hybrid. We postulate that meiotic drive elements might underlie an explanation of Haldane's rule, whereas cytoplasmic sex ratio distorters are involved in the second class of hybrid disruption. These two classes are discussed separately. First, we discuss meiotic drive genes. We show that drive elements and their suppressors are more likely to originate and accumulate on the sex chromosomes than on autosomes. When *X* and *Y* chromosomes from different species are brought together in interspecific hybrids, the incompatibility of driving elements and suppressors can result in the sterility or absence of the heterogametic sex. Further we show that the reported taxonomic distribution of meiotic drive matches the distribution of taxa which obey Haldane's rule. Second, we discuss the invasion of cytoplasmic sex ratio distorters and their subsequent suppression by nuclear genes. Examples of the possible involvement of cytoplasmic genes in sex ratio distortion are outlined.

MEIOTIC DRIVE GENES AND THEIR DISTRIBUTION

The process of meiosis is often fair but selfish genes are favored if they try to subvert meiosis and enhance

their own transmission (meiotic drive). For example, males in *Drosophila melanogaster* that are heterozygous for the Segregation Distorter (*SD*) chromosome produce virtually only *SD*-carrying offspring due to the failure of non-*SD*-carrying sperm to mature (HARTL, HIRAIZUMI and CROW 1976).

Meiotic drive occurs on autosomes but has been more frequently reported on sex chromosomes in the heterogametic sex, where drive causes a distortion in the sex ratio (Table 1). For instance there are numerous reports of meiotic drive sex ratio distorters in *Drosophila* species (*e.g.*, *Sr*, *sr*, *RD*, *T(1;4)B^s*, *sc^4-sc^8* and *msr*) but very few of autosomal drivers (*e.g.*, *SD*). Similarly in the Lepidoptera there are several instances of sex chromosome drive but only one autosomal (Table 1). What is noticeable about the list of organisms with meiotic drive is that reports of drive are largely limited to well studied organisms; the implication is that drive probably afflicts many other organisms but an intense study is needed to adequately document it.

The higher frequency of reports of sex chromosome drive could be for the artefactual reason that autosome drive is easily overlooked because it does not result in any obvious phenotypic difference in offspring. Alternatively, drive elements may be more likely to become established and persist in an active form on sex chromosomes than on autosomes. We develop simple population genetic models of drive to demonstrate this. They show that the primary reason for drive being associated with sex chromosomes is the low frequency or complete absence of recombination between the *X* and *Y* chromosomes.

Our principle concern is to contrast the conditions for invasion of drive elements on autosomes and sex chromosomes. But we will also consider whether insensitive sites and modifiers are favored, and how this affects the likelihood of drive elements persisting through time. The analysis is based on the standard procedures developed by PROUT, BUNDGAARD and BRYANT (1973), THOMPSON and FELDMAN (1975), CHARLESWORTH and HARTL (1978) and others, to study the population dynamics of drive elements and their modifiers.

Model: The models consist of two loci with arbitrary linkage in an infinite diploid population with separate sexes. Taking Drosophila as our "animal in mind," the analysis assumes that drive occurs only in males (the heterogametic sex) and recombination only in females (the homogametic sex). We also consider the reverse case of drive in the homogametic sex. Imagine that the drive element is active during spermatogenesis. It causes either chromosome breaks in its homolog, marking of its homolog or marking of the opposite pole in meiosis I in some way that results in gamete failure. In whatever way drive is caused, the result is that individuals heterozygous for drive produce a disproportionate fraction of functional gametes containing the drive element.

In those systems studied in detail, drive results from the interaction between two genetic loci: the drive locus itself (*D*) and the site sensitive to its action (*I*). Each locus has two alleles, where lower case designates the wild-type allele: *D*, *d* and *I*, *i*. *D* chromosomes are capable of causing drive, whereas *d* are not. Three conditions must be met for production of the drive phenotype. First, the homologous chromosome must be a responder that is sensitive to the drive element (*i*). Second, the drive element must not drive against itself. Self-tolerance is achieved if the drive element is linked to an insensitivity allele (*I*). The key assumption here is that the insensitivity allele suppresses drive in *cis* but has no effect in *trans*. The existence of separate, albeit closely linked, drive and sensitivity loci is known for *SD* in Drosophila and for *t* in mice. In both cases the insensitivity allele acts only in *cis* (FRISCHAUF 1985; SANDLER and GOLIC 1985). Finally, the two loci must map to the same chromosome. If they do not, the gametic distortion caused will not preferentially affect the drive element itself.

Classically drive chromosomes (*DI*) drive against wild-type chromosomes (*di*). Let *K* be the fraction of a *DI/di* heterozygote's gametes that are *DI*. If $K = 0.5$ there is no drive. If $K = 1.0$ drive is complete and all of the *di* homologs are excluded from mature gametes. Usually the *D* and *I* loci are tightly linked. However recombination will generate *Di* and *dI* chromosomes. The former are "suicide" chromosomes which drive against themselves (HARTL 1974). Let $1 - L$ be the fraction of a *Di/dI* gametes that are *Di*. For simplicity we assume that $L \approx 1$ and all "suicide" chromosomes self destruct. *dI* are insensitive chromosomes that cannot be driven against but do not themselves drive. The recombination rate between drive and sensitivity loci is *r*. A full description of the effects of drive on gametic ratios is given in Table 2.

Drive causes a reduction in the number of mature sperm and a consequent reduction in fertility. Reduction in ejaculate size by half need not result in a halving in fertility but does in general reduce fertility (HARTL 1972). For example, the *X*-linked drive agent in Drosophila is known to decrease fertility by reducing ejaculate size and lowering sperm displacement in already mated females (WU 1983). In addition, drive is taken to be an active process that carries a fitness cost. So even if gametic ratios are not distorted, say because the homolog is insensitive to drive, the individual has reduced fitness. These fitness affects will be modeled by setting the fertility of drive heterozygotes to $1 - U$. Drive homozygotes have variable fitness. Many are lethal, due to linkage with recessive lethals (HIRAIZUMI 1962; HARTL 1973). Others are

TABLE 1

Possible incidences of meiotic drive in animals with sex chromosomes

Organism	Name of drive	Type of drive	Reference	Comments
Diptera				
Drosophila paramelanica	*Sex ratio*	*X* drive	STALKER (1961)	
D. mediopunctata	*Sex ratio*	*X* drive	DE CARVALHO, PEIXOTO and KLACZKO (1989)	
D. quinaria	*Sex ratio*	*X* drive	JAMES and JAENIKE (1990)	*X* drive suspected
D. testacea	*Sex ratio*	*X* drive	JAMES AND JAENIKE (1990)	
D. pseudoobscura	*Sex ratio*	*X* drive	STURTEVANT and DOBZHANSKY (1936)	
D. pseudoobscura	*Male sex ratio*	Nondisjunction	COBBS (1986)	
D. persimilis	*Sex ratio*	*X* drive	WU and BECKENBACH (1983)	
D. obscura	*Sex ratio*	*X* drive	GERSHENSON (1928)	
D. affinis	*Sex ratio*	*X* drive	VOELKER (1972)	
D. affinis	*Male sex ratio*	*Y* drive	VOELKER (1972)	
D. subobscura	*Sex ratio*	*X* drive	HAUSCHTECK-JUNGEN and MAURER (1976)	
D. athabasca	*Sex ratio*	*X* drive	MILLER (1971)	
D. azteca	*Sex ratio*	*X* drive	DOBZHANDKY and SOCOLOV (1939)	
D. sulfurigaster albostrigata	*Sex ratio*	*X* drive	WILSON *et al.* (1969)	Drive suspected
D. simulans	*sxr*	*X* drive	FAULHABER (1967)	Recessive drive
D. melanogaster	Barr-Stone	*X* drive	NOVITSKI and SANDLER (1957)	Artificially produced
D. melanogaster	*RD*	*X* drive	NOVITSKI and HANKS (1961)	Artificially produced
D. melanogaster	sc^4-sc^8	*X* drive	GERSHENSON (1933)	Artificially produced
D. melanogaster	*SD*	Autosomal	SANDLER and GOLIC (1985)	Male specific
D. melanogaster	Unnamed	*X* drive	CURTISINGER (1984)	
D. melanogaster	*SD/Y*	*Autosome vs. Y* drive	LYTTLE (1989)	Artificially produced
Aedes aegypti	$D(M^D)$	*Y* drive	WOOD and NEWTON (1977)	Driver is dominant
Culex pipiens	*Md/md*	*Y* drive	SWEENEY and BARR (1978)	Driver is recessive
Musca domestica	Unnamed	*X* drive	FOOT (1972), WAGONER (1969)	Drive suspected
Glossina morsitans	Unnamed	*X* drive	GOODING (1986), RAWLINGS and MAUDLIN (1984)	Drive suspected
Lepidoptera				
Acraea encedon	Unnamed	*Y* drive	OWEN (1970)	
Maniola jurtina	Unnamed	*Y* drive	SCALI and MASETTI (1973)	Drive suspected
Danaus chrysippus	Unnamed	Autosomal	SMITH (1976)	Drive suspected-female specific
D. chrysippus	Unnamed	*Y* drive	SMITH (1975)	Drive possible (though male killing is also suspected)
Philudoria potatoria	Unnamed	*Y* drive	MAJERUS (1981)	Drive probable
Mylothris spica	Unnamed	*X* and *Y* drive	POULTON (1928)	Drive possible
Abraxus grossulariata	Unnamed	O *vs. X* drive	DONCASTER (1913, 1914)	
Talaeporia tubulosa	Unnamed	*X vs.* O and O *vs. X*	SEILER (1920)	Effect is temperature dependent
Hemiptera				
Tetraneura ulmi	Unnamed	*X vs.* O	SCHWARTZ (1932)	*X/O* drive in males is characteristic of aphids (see WHITE 1973)
Mammals				
Mus musculus	*T/t*	Autosomal	KLEIN (1986)	Male specific
M. musculus	Unnamed	*X vs.* O	KAUFMAN (1972)	Unusual *XO* females with drive
M. musculus	Unnamed	Autosomal	AGULNIK, AGULNIK and RUVINSKY (1990)	Chromosome *1* drive in females
M. castaneus	*T/t*	Autosomal	KLEIN (1986)	Male specific
M. molossinus	*T/t*	Autosomal	KLEIN (1986)	Male specific
M. domesticus	*T/t*	Autosomal	KLEIN (1986)	Male specific
Dicrostonyx torquatus	Unnamed	*Y* drive	GILEVA (1987)	Male specific
Myopus schistocolor	*Y* drive	*X* drive	GROPP *et al.* (1976)	
Microtus oregoni	*Y* drive	*X* and *Y* drive	OHNO, JAINCHILL and STENIUS (1963)	Females (*XO*) produce only *X* eggs, males (*XY*) produce *Y* or O sperm
Homo sapiens	Alport's syndrome	Autosomal	SHAW and GLOVER (1961)	
H. sapiens	Holt-Oram syndrome	Autosomal	GALL *et al.* (1966)	
Birds				
Falco tinnunculus	Unnamed	*X* and *Y* drive	DIJKSTRA, DAAN and BUKER (1990)	Birds discussed in MAYR (1939) and CREW (1937)
Gallus gallus	Unnamed	*X* and *Y* drive	CREW (1938)	
Fish				
Poecilia reticulata	Unnamed	*X* drive	FARR (1981)	Drive suspected

not linked to recessive lethals and are fully viable as homozygotes, though the majority of these are sterile (TEMIN and MARTHAS 1984; LYON 1986). Owing to this variability, we set the fertility of drive homozygotes to $(1 - U)^*$ relative to wild type (Table 2).

The sensitivity locus has fitness consequences as well. We consider two types of insensitivity at the *I* locus. (1) "Passive" insensitivity is cost free. An example of passive insensitivity is the absence of a recognition site for the drive agent. (2) In contrast, "active" insensitivity carries a cost. Costs might arise because suppression is caused by the production of some substance (*e.g.*, RNA, protein) that inhibits the drive agent or because the absence of a recognition site corrupts a normal coding or binding function. *SD* provides an example of such a cost; in the absence of

TABLE 2

Phenotypes, gametic ratios and fertility under autosomal drive

Chromosome genotype and phenotype		Gametic ratio (above) and fertility (below) with different homologs			
		di Wild type	*dI* Insensitive	*Di* Suicide	*DI* Drive
di	Wild type	0.5 1	0.5 $1 - S$	0.5 $1 - U$	$1 - K$ $1 - U$
dI	Insensitive	0.5 $1 - S$	0.5 $(1 - S)^2$	L $1 - U$	0.5 $(1 - U)(1 - S)$
Di	Suicide	0.5 $1 - U$	$1 - L$ $1 - U$	0	$(1 - U)$*
DI	Drive	K $1 - U$	0.5 $(1 - U)(1 - S)$	L $(1 - U)$	0.5 $(1 - U)$*

SD, selection favors the wild type over the insensitivity allele by about 15% per generation (WU, TRUE and JOHNSON 1989). We consider the fitness loss to be experienced both in the presence and absence of drive elements. Active modifiers reduce heterozygote fitness by $1 - S$ and homozygote fitness by $(1 - S)^2$ in the absence of drive elements (Table 2). The cost of drive considered above is assumed to contain the cost of self-suppression. In general, we assume that suppression is less costly than drive, $U > S$, though this need not be the case.

In *SD* and other drive systems there are also a number of other loci that enhance or suppress the degree of distortion produced by the drive agent. These loci are called modifiers. Unlike the sensitivity locus, modifiers are found on all chromosomes and their action takes place in both *cis* and *trans*. Nonetheless, selection for modifiers closely follows that for insensitive sites. Let the modifier locus have two alleles, M that reduces the intensity of distortion and m that does not. We assume that M is dominant. Like sensitivity alleles, modifiers may have fitness affects and so can be classified as either (i) passive (*i.e.*, cost free) or (ii) active (*i.e.*, costly). The latter reduce fitness by $1 - J$ compared to wild type. The rate of recombination between the modifier and the drive locus is r.

Drivers on autosomes: Consider first the evolution of drive elements on autosomes. A drive element that arises on a chromosome that is a responder at the I locus will drive against itself as much as against its homologue and so merely cause reduced fertility. It will quickly be eliminated. Alternatively, the drive element arises on a chromosome already insensitive to drive. If the insensitivity allele is at a low frequency then the condition for the drive element to spread when rare is given approximately by the fitness of a drive chromosome on a wild-type background compared to the fitness of the wild-type chromosome, $W(A^{DI}A^{di}) > W(A^{di}A^{di})$. $W(A^{xy}A^{ij})$ is the fitness of an A^{xy} chromosome when coupled with an A^{ij} chromosome. On the assumption of a 1:1 sex ratio, each genotype spends an equal time in females and males. Female fitness of the A^{xy} chromosome in an $A^{xy}A^{ij}$ genotype is subject to recombinational loss, at a rate r, if $x \neq i$ and $y \neq j$. Male fitness is determined by the gametic ratios and fertility given in Table 2. Substituting and rearranging gives,

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

This inequality was first derived by CHARLESWORTH and HARTL (1978; Equation 3). Invasion occurs if the fertility cost of drive (U) is less than the benefit of greater segregation (K), factored by the loss of drive elements in recombinants lacking the insensitivity allele. This condition requires that the insensitivity allele is rare.

If the insensitivity allele is initially common when drive is introduced into the population then many homologs will already be able to suppress drive. The chances that the drive element is favored are greatly diminished as the initial frequency of the insensitivity allele is increased. Let γ be the frequency of insensitivity. The drive element is favored if the fitness of a drive chromosome coupled to wild-type and insensitive chromosomes, at frequency γ and $1 - \gamma$, respectively, is greater than the fitness of these nondriving chromosomes coupled to each other. Assuming that the cost of suppression is small ($S \approx 0$), the drive element invades if,

$$\gamma W(A^{DI}A^{dI}) + (1 - \gamma)W(A^{DI}A^{di}) > W(A^{di}A^{di}).$$

Assuming an equal sex ratio and substituting for the male fitness terms in Table 2, gives after some rearrangement,

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

The condition for the spread of the drive element is

negatively related to the frequency of insensitivity alleles. As insensitivity to drive becomes more common (large γ) either the drive element must cause greater distortion of segregation (*i.e.*, $K \rightarrow 1$) or drive must be less costly ($U \rightarrow 0$) for invasion.

The degree of physical linkage between the drive and sensitivity loci is also important in determining the probability that drive spreads. When drive is rare most drive chromosomes occur in females as heterozygotes ($A^{DI}A^{di}$). A fraction r of the gametes will be recombinants, half lacking the drive element (A^{dI}) and half lacking the insensitivity allele (A^{Di}). The latter are "suicide" chromosomes that drive against themselves.

If the drive and sensitivity loci are widely dispersed or on different chromosomes then $r \approx 0.5$. Half the drive elements will be lost through crossing over creating "suicide" recombinants that drive against themselves. This strongly selects against the spread of the drive element. We note that if recombination also occurs in the heterogametic sex, selection against weakly linked drive and modifier loci will be even stronger as "suicide" recombinants will be produced in both sexes.

Conversely, if the drive and sensitivity loci are closely linked, recombinant loss will be small. The most permissive case occurs when the driver and sensitivity map to the same genetic locus and $r = 0$. It is significant then that the drive and responder loci in the *SD* system are tightly linked and the rate of crossing over between them is very low (HARTL 1974). Similarly, there are at least four different genetic rearrangements in the mouse *t* complex that all have the effect of suppressing recombination with wild-type chromosomes in this region (ARTZT, SHIN and BENNETT 1982; PLA and CONDAMINE 1984; HERMANN *et al.* 1986; SARVETNICK *et al.* 1986; HAMMER, SCHIMENTI and SILVER 1989).

In summary, autosome drive is only likely to invade if insensitivity to its action is rare and the rate of recombination between drive and sensitivity loci is very low. Rarity may result from a recent origin, but then we require the highly unlikely condition that both the drive element and insensitivity allele arose at the same time *and* on the same chromosome. Alternatively, rarity may be due to the insensitivity allele being costly and selected against; yet this cost cannot be too large for otherwise the allele would be eliminated. A third possibility is that the *DI* chromosome enters the population as an immigrant, though this begs the question of its establishment in the first place.

Assuming that these conditions are met, the drive locus can rise in frequency to fixation or polymorphism. Fixation is unlikely. It requires that drive homozygotes do not have *greatly* reduced fertility (*e.g.*, $(1 - U)^* > (1 - U)^2$ in Table 2). If the fitness of drive homozygotes drops more than multiplicatively then strong frequency-dependent selection will limit the increase in frequency of drive, resulting in polymorphism. Such fitness effects are known in *SD* and *t*, where drive homozygotes are often infertile, though not always (KETTANEH and HARTL 1980; LYON 1986).

Another reason why fixation is unlikely is the existence of nondriving chromosomes able to suppress drive. As we have discussed previously, recombination between wild-type and drive chromosomes will generate *dI* chromosomes that cannot drive but are insensitive to drive elements on homologs. Even if drive and sensitivity map to the same locus, insensitive chromosomes are likely to arise through mutational loss of the drive function. A population with drive at high frequency is always susceptible to invasion by chromosomes that suppress drive but do not incur its costs.

If insensitivity is passive (cost free), then it will rise in frequency and cause the elimination of drive elements. If insensitivity is active (costly) polymorphism results. Insensitivity is selected when drive is common if the cost of suppressing drive is less than the cost of drive itself. Assuming multiplicative fitness, $(1 - U)^* = (1 - U)^2$ in Table 2, all that is required is that $S < U$. But active insensitivity is subject to strong frequency-dependent selection. Wild-type chromosomes (*di*) will invade once insensitivity reaches a high frequency, because the wild type avoids the costs of suppressing drive. In turn, the presence of wild-type chromosomes maintains drive in the population.

In addition there may be modifiers which suppress drive. Modifiers linked to the driven chromosome are favored if they improve its ability to resist drive. Unlinked modifiers are also favored because drive tends to reduce the number of mature gametes and thereby reduce the fitness of all chromosomes. This is particularly so in cases where drive homozygotes have severely reduced fitness. This is the case in *SD* where suppressing modifiers are found on the *X* chromosome in natural populations and on chromosomes *3* and *4* in laboratory studies which protect against the fertility reducing effects of *SD* (LYTTLE 1979; GOLIC 1990).

The conditions favoring modifiers that suppress drive are similar to those of the insensitivity allele. They have been investigated by a number of workers (*e.g.*, PROUT, BUNDGAARD and BRYANT 1973; THOMPSON and FELDMAN 1976) who have specified the conditions for polymorphism on the assumption that drive is a one locus system (*i.e.*, $D = DI$ and $d = di$) and modifiers are passive. The complexities of these models lie beyond our interests. But we note that like insensitivity alleles, modifiers are more likely to be established if (a) they are closely linked to the drive locus (*i.e.*, r is small) or (b) they reduce the cost of suppressing drive or (c) they increase the suppression of distortion (when the insensitivity allele only confers

TABLE 3

Phenotypes, gametic ratios and fertility under sex chromosome drive

X-drive (or *Y*-drive) chromosome genotype and phenotype		Gametic ratio (above) and fertility (below) with sensitive *Y* (or *X*) chromosome
di	Wild type	0.5 1
dI	Insensitive	0.5 $1 - S$
Di	Suicide	$1 - L$ 1
DI	Drive	K $1 - U$

partial resistance). Autosomal drive agents can be maintained in functional form with modifiers, mainly on homologs, though also on other chromosomes. The exact frequency of autosomal drive will be dependent on the details of the system in question, though it appears from surveys that the frequency of drive in natural populations is quite low (HARTL 1975; KLEIN 1986). Finally we observe that if drive occurs in the homogametic sex rather than the heterogametic sex, the qualitative nature of these results does not differ.

Drivers on sex chromosomes: The analysis above suggests that the conditions for the spread and persistence of drive elements on autosomes are very stringent. The reverse is true for sex chromosomes. As before consider drive in the heterogametic sex, either *Y* drive against *X* or *X* drive against *Y*. The main difference between sex chromosomes and autosomes is the absence of recombination between the *X* and *Y*. In many male heterogametic species male meiosis is achiasmate (JOHN 1990; BURT, BELL and HARVEY 1991), and where crossing over between *X* and *Y* does occur, chiasmata are typically limited to the chromosome tips, leaving the bulk of the chromosome unrecombined (ALBERTS *et al.* 1989, p. 581; JOHN 1990). The absence of recombination means that insensitive sites on the *X* cannot be moved by recombination to the *Y* or *vice versa*. This allows some simplification of the table of gametic ratios and fertility (Table 3).

As with autosomes, a drive element that arises on a sex chromosome lacking the insensitivity allele will drive against itself and quickly be eliminated. Drive elements will only spread if they are coupled to insensitivity alleles. Given this, consider the spread of a *Y*-linked drive element. As the *Y* never recombines, the condition for invasion, assuming that the cost of suppression is small ($S \approx 0$), is simply that the fitness of a driving *Y* chromosome is greater than that of its wild type, $W(Y^{DI}X^{i}) > W(Y^{di}X^{i})$,

$$U < 1 - \frac{1}{2K}. \tag{3}$$

For *Y*-linked drive it does not matter whether the insensitivity allele is at high or low frequency so long as the drive and insensitivity are on the same chromosome. We note that this equation is the same as Equation 1 for the invasion of autosome drive when there is no recombination ($r = 0$). For *X*-linked drive the condition for the spread of the drive element is *positively* related to the frequency of insensitivity. Let γ be the frequency of the *X*-linked insensitivity allele. Given a 1:1 sex ratio, *X* chromosomes occur twice as frequently in females than in males. Assuming that the cost of suppression is small ($S \approx 0$), *X*-linked drive invades if,

$$2\gamma W_f(X^{DI}X^{dI}) + 2(1-\gamma)W_f(X^{DI}X^{di}) + W_m(X^{DI}Y^{i}) > 2W_f(X^{di}X^{di}) + W_m(X^{di}Y^{i}),$$

where W_f and W_m denote the fitness of chromosome pairs in females and males respectively. Computation of this gives,

$$U < 1 - \frac{(1 + 2r(1-\gamma))}{2K}. \tag{4}$$

If insensitivity is at high frequency this favors the spread of the drive element. The higher the frequency of insensitivity the lower the probability that the drive chromosome ever couples with a wild-type *X* and the lower the chances of recombination producing "suicide" chromosomes (X^{Di}). There is no requirement, as there is in the autosome case, that insensitivity has recently entered the population or that it is subject to weak negative selection. Further, if insensitivity is at fixation there is no requirement for the drive element to be closely linked. Conditions (Equations 3 and 4) show that attainment of self-suppression is unlikely to be a problem in sex chromosome drive in contrast to the special conditions required for autosomes.

Given that a sex-linked drive element invades, we can now consider the spread and location of modifiers that suppress drive. Drive on sex chromosomes causes alteration to the offspring sex ratio; *Y*-linked drive producing male biased broods and *X*-linked drive producing female biased broods. As sex-linked drive elements spread the population sex ratio becomes increasingly biased. In principle this could lead to extinction (HAMILTON 1967; HEUCH 1978). More plausibly modifiers that suppress drive are selected for.

These modifiers can map to anywhere in the genome: either on autosomes or on the sex chromosome driven against (ESHEL 1975). They are favored on autosomes because drive causes a biased and nonoptimal sex ratio. Say *X*-linked drive is common. Then the population sex ratio will be female biased (if male heterogametic). A nonmodifying autosome will consequently be found predominantly in females. In contrast, an autosome with a modifier suppressing drive

TABLE 4

Modifier action under sex chromosome drive

X-drive (or Y-drive) chromosome genotype and phenotype		Gametic ratio (above) and fertility (below) when coupled to suppressing modifiers[a]			
		Y-linked (or X-linked)		Autosome linked	
		m Wild type	*M* Suppressor	*mm* Wild type	*Mm* or *MM* Suppressor
di	Wild type	0.5 1	0.5 $1 - J$	0.5 1	0.5 $1 - J$
dI	Insensitive	0.5 $1 - S$	0.5 $(1 - S)(1 - J)$	0.5 $1 - S$	0.5 $(1 - S)(1 - J)$
Di	Suicide	$1 - L$ 1	0.5 $1 - S$	$1 - L$ 1	0.5 $1 - J$
DI	Drive	K $1 - U$	0.5 $(1 - U)(1 - J)$	K $1 - U$	0.5 $(1 - U)(1 - J)$

[a] Homologous sex chromosome is assumed to be sensitive.

will be equally distributed between males and females. As a male has higher reproductive value than a female in a population with a female biased sex ratio, autosome linked modifiers will have higher fitness. Modifiers on the sex chromosome driven against are favored for this and the additional reason that they are on chromosomes normally excluded from gametes by the drive agent. The fertility and gametic ratios of sex drive genotypes subject to modifiers are given in Table 4.

Intuition leads us to expect modifiers of sex-linked drive to be found predominantly on the sex chromosome driven against but also on autosomes. We can show this formally by considering the conditions for the spread of autosome and sex-linked modifiers. In calculating the advantage of a modifier we must consider the population sex ratio. Taking the optimal sex ratio as 1:1, the reproductive value of a male relative to a female can simply be approximated as,

$$R_m = \frac{1 - p}{p}, \qquad R_f = 1, \tag{5}$$

where p is the frequency of males in the population. If males are rare $R_m > 1$. If they are common $R_m < 1$. The value of p can be estimated from the frequency of drive elements. Let α be the frequency of the Y-linked drive elements in adult males giving rise to gametes. As drive occurs in α males, the proportion of offspring that are male is $1 - \alpha + 2K\alpha$, and the value of R_m in the next generation is,

$$R_m = \frac{1 + \alpha - 2K\alpha}{1 - \alpha + 2K\alpha}. \tag{6a}$$

This can be simplified on the assumption of complete drive, $K = 1$,

$$R_m = \frac{1 - \alpha}{1 + \alpha}. \tag{6b}$$

Similar functions apply for X-linked drive, except that α now measures the frequency of X-linked drive elements.

For simplicity we assume that the modifier completely suppresses the action of the drive agent. The maximum cost of a modifier (J) that permits invasion will be an increasing function of the frequency of drive (α). An analytical solution is easy to derive on the assumption that the frequency of drive is constant across generations and hence the sex ratio and reproductive value of each sex also remain constant. In these calculations, the reproductive value of offspring must be considered, as one of the benefits of suppressing drive is an unbiased sex ratio. Assuming that there is complete drive, $K = 1$, for invasion the fitness of X-linked modifiers to Y-drive must exceed that of the wild-type, nonmodifying X,

$$\alpha W(X^M Y^{DI}) + (1 - \alpha)W(X^M Y^{di}) > \alpha W(X^m Y^{DI}) + (1 - a)W(X^m Y^{di}),$$

and for Y-linked modifiers of X-drive,

$$\alpha W(Y^M X^{DI}) + (1 - \alpha)W(Y^M X^{di}) > \alpha W(Y^m X^{DI}) + (1 - \alpha)W(Y^m X^{di}).$$

Substituting for the fertilities and gametic ratios given in Table 4, in both cases the maximum cost of a modifier must satisfy,

$$J < \frac{\alpha(1 - U)}{1 - U\alpha}. \tag{7a}$$

A comparable calculation can be made for autosome modifiers of Y-drive and X-drive, respectively (abbreviating $A^M A^m$ as A^M, and $A^m A^m$ as A^m),

$$\alpha W(A^M Y^{DI} X^i) + (1 - \alpha)W(A^M Y^{di} X^i) > \alpha W(A^m Y^{DI} X^i) + (1 - \alpha)W(A^m Y^{di} X^i),$$

$$\alpha W(A^M X^{DI} Y^i) + (1 - \alpha)W(A^M X^{di} Y^i)$$

$$> \alpha W(A^m X^{DI} Y^i) + (1 - \alpha) W(A^m X^{di} Y^i).$$

Both yield the same condition for the invasion of autosome linked modifiers,

$$J < \frac{\alpha^2(1 - U)}{1 - U\alpha}. \quad (7b)$$

These relationships have been checked by simulation, in which the assumptions above are relaxed and the frequency of the drive element is allowed to evolve (Figure 1).

For both *X*-linked and *Y*-linked drive the condition for the spread of modifiers becomes less restrictive as the frequency of the drive element increases. Selection is frequency-dependent because the probability that a modifier encounters a drive element and the benefit of suppressing drive increase as the drive element spreads and the sex ratio becomes increasingly biased. Not only will passive (cost free) modifiers be favored but also active modifiers that carry considerable cost. In both cases selection on sex-linked modifiers is stronger than on autosome linked modifiers at low frequencies of the drive element. This is because the sex ratio is not greatly distorted when drive is rare, so there is little benefit for autosome modifiers. However, as the drive element rises in frequency, selection on the sex ratio comes to dominate, and autosome linked modifiers are equally favored as drive approaches fixation. We expect that modifiers of sex chromosome drive will be frequently located on the complementary driven *Y* or *X* chromosome and to a lesser degree on autosomes, though this relationship will be somewhat curtailed if there are more potential modifier sites on autosomes. This expectation agrees with the known distribution of sex chromosome drive modifiers, which are found on both the driven chromosome and autosomes (ZIMMERING 1960; COBBS 1987; WU and HAMMER 1991).

If suppression is active then the modifier will not go to fixation because its advantage declines as the frequency of the drive element falls. As with autosome drive, at equilibrium there will be polymorphism at the drive locus (drive and wild-type chromosomes) and at the modifier locus (modifier and wild-type chromosomes). However, a wider range of modifiers are possible. Modifiers of sex chromosome drive may be located anywhere in the genome. In addition, selection for modifiers is weaker in autosome drive. First, because autosome drive does not usually cause sex ratio disturbance. Second, because autosome drive modifiers will only invade if the cost of suppression is less than the cost of drive. Such a constraint does not operate on modifiers of sex chromosome drive, where the cost of suppression can exceed the cost of drive because of the effect of sex ratio disturbance.

None of the above considerations applies to *X*-linked drive elements that cause drive in the homogametic sex (*i.e.*, *X* drive against *X*). Drive by *X* chromosomes in the homogametic sex is subject to the same constraints as autosome drive in the heterogametic sex, principally because drive and insensitivity alleles on the *X* chromosome can recombine. Although we have not formally modeled this, the rate of evolution of *X*-linked and autosome linked drive in the homogametic sex should be quantitatively similar to the rate of evolution of autosome linked drive in the heterogametic sex. Similarly, the range of modifiers that suppress drive in the homogametic sex will be the same as those that suppress autosome drive in the heterogametic sex. In both cases modifiers on nonhomologuous chromosomes can be selected for because of the reduction in fertility caused by drive. However, as drive in the homogametic sex cannot cause sex ratio disruption, this is the only force selecting for nonhomologous modifiers. So we do not ex-

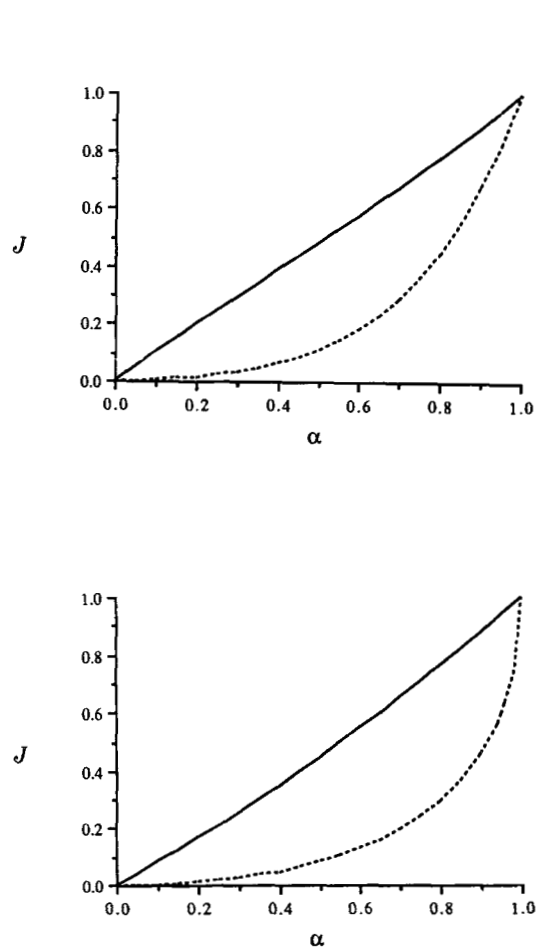

FIGURE 1.—The maximum cost (J) for invasion of a sex-linked (solid line) or autosome linked (dotted line) modifier plotted against the frequency of the drive element (α): for (a) *Y*-linked drive, and (b) *X*-linked drive. These plots are derived from simulation. Invasion was considered to take place if the frequency of a rare modifier (10^{-5}), introduced at random by mutation, increased after two generations. Similar relationships hold over longer time periods. Drive was complete ($K = 1$) and the cost of drive was set at $U = 0.5$; values at which the frequency of drive barely changed.

pect a preponderance of *X*-linked drive in the homogametic sex. Neither do we expect sex chromosome drive systems in the homogametic sex to evolve as quickly as they do in the heterogametic sex.

Summary: We can summarize these results as follows. The conditions for the initial spread and persistence of active drive elements on autosomes are very restrictive, while those for sex chromosomes are much more permissive. For drive to spread on autosomes it must occur linked to a rare insensitivity site that stops self-drive, preferably in close linkage. This is highly unlikely, requiring either that the drive and insensitivity arise at the same time or that the insensitivity allele is costly, albeit not too costly for otherwise it would already have been eliminated. Linkage however can be made more likely by the presence of an inversion preventing crossing over across its length.

In contrast, insensitivity need not be at low frequency for sex chromosome drive to spread. Rather, it is better if insensitivity has already gone to fixation. There is no need for close linkage between drive and insensitivity loci on the *Y* chromosome because of the absence of recombination, and little advantage on the *X* chromosome, unless insensitivity is at low frequency. Not only will drive be more readily established on the sex chromosomes but there will be higher turnover of variant drivers and suppressors. Finally, a greater range of drive suppressing modifiers are likely to evolve in response to *X* or *Y* drive because of the distortion to the sex ratio. As the drive element spreads, the population sex ratio becomes increasingly imbalanced, and selection in favor of modifiers increases. Such active modifiers do not spread to fixation and nor do they eliminate drive. Rather a polymorphic equilibrium will result at both drive and modifier loci. As with autosome systems, the equilibrium frequency of drive and its modifiers will depend on the details of the system being considered.

Finally, we note that conditions for the evolution of sex chromosome drive in the homogametic sex will resemble those governing autosome drive in the heterogametic sex. There is no expectation that drive systems will evolve more rapidly on autosomes than on the sex chromosomes because all chromosomes in the homogametic sex can recombine. In addition, we expect that homogametic drive (*X* or autosome) will evolve at a rate similar to that of autosome drive in the heterogametic sex, other things being equal.

Meiotic drive and Haldane's rule: In recently diverged species it is likely that novel drive systems will evolve more quickly on the sex chromosomes of the heterogametic sex. This has the interesting side effect that in interspecific hybrids the drive elements, insensitivity alleles and suppressors found on the *X* and *Y* chromosomes of different species will be incompatible. All that is required is that control is specific to a particular drive system. So if there has been evolutionary change in the drive system in one species (*i.e.*, coevolution of both the drive element and its suppressors), both directions of hybrid cross will give rise to incompatible combinations of *X* and *Y* chromosomes. So long as both sex chromosomes attempt to drive, this incompatibility ensures that there are no constraints on either *X*-linked or *Y*-linked drive in hybrids. Hence in spermatogenesis no sperm will mature if the male is the heterogametic sex, and in oogenesis no eggs will mature if the female is the heterogametic sex. That sterility can arise through chromosomes driving against each other causing mutual disruption is supported by the very low fertility reported in some males made heterozygous for different *SD* chromosomes (KETTANEH and HARTL 1980) or for different *t* haplotypes (LYON 1986).

In contrast, sterility in the homogametic sex is not expected to show any strong linkage to the sex chromosomes. Drivers on *X* chromosomes are as likely to evolve as drivers on autosomes. In addition, we have shown that homogametic sex chromosome drive systems evolve at a much slower rate than heterogametic sex chromosome drive systems, on the same time scale as autosome drive in the heterogametic sex. This leads to the prediction that homogametic sex sterility will evolve at a much slower rate than heterogametic sex sterility. This prediction is broadly consistent with the known distribution of sterility factors (COYNE and ORR 1989).

Systems vulnerable to drive are likely to evolve means to protect themselves. One form of general protection is the destruction of all gametic products of a meiotic event if either *X* or *Y* attempts to drive (HAIG and GRAFEN1991). Under such a constraint, a successful driver must not only be insensitive to its own action but also capable of undermining these general anti-drive precautions. In the context of a hybrid a driver might not only be derepressed but also be incapable of avoiding the general anti-drive defences, triggering mutually assured destruction and thus causing sterility. As *X* and *Y* are particularly susceptible to drive they may be highly sensitive to any unusual behavior of their homolog during meiosis, so that gamete failure may occur even in the absence of attempted drive.

Haldane's rule however, not only covers the sterility of the heterogametic sex but also their inviability and absence. How can this be reconciled with the notion of meiotic drive, which up to now we have discussed as though it only affected gametogenesis? We suggest that an explanation may be found in the suggestion that meiotic drive is caused by transposable elements (GOLIC 1985, 1990; SANDLER and GOLIC 1985; HICKEY, LOVERRE and CARMODY 1986). Even if this hypothesis is not confirmed, we believe it serves as a

useful guide to the type of mechanism that might underlie drive element induced viability loss.

Transposable elements are selfish genetic elements that enhance their own transmission frequency by inserting copies throughout the genome. HICKEY, LOVERRE and CARMODY (1986) propose that some of these elements cause meiotic drive by producing copies that preferentially insert into the homologous wild-type chromosome. These inserted copies then disrupt the normal functions of the wild-type chromosome resulting in sperm dysfunction and meiotic drive. Usually the activity of transposable elements is suppressed and transposition occurs only at a low rate. But in hybrid dysgenic crosses (male strain with transposable elements *x* female strain with none) there is a marked increase in transposition events both in the germline *and* somatic tissues, and the latter can cause high embryo inviability and mortality (FINNEGAN and FAWCETT 1986). Since somatic transposition gives no obvious advantage to the transposable element, because these elements are vertically transmitted, it presumably occurs as an unselected side effect when suppression is absent.

We do not suggest that all elements which cause hybrid dysgenesis are also meiotic drive elements, but rather that if transposable elements cause meiotic drive they might also be activated during embryogenesis in heterogametic hybrids and thereby cause high embryo mortality. Alternative models of meiotic drive consider the possibility that the protein product of the drive locus disrupts the maturation of any chromosome with the necessary sensitivity locus (TEMIN *et al.* 1991). Should this protein be transcribed and capable of harming cells prior to gametogenesis then it could also account for the inviability or absence of the heterogametic sex.

We have presented above a simplified view of meiotic drive and its various costs. This general model may not necessarily be directly applicable in individual cases. For instance, there is a modifier of *t* haplotypes which renders a chromosome insensitive to male transmission ratio distortion (TRD) which causes "reverse drive" in wild-type chromosomes, being transmitted to only 20% of gametes in males (DUNN and BENNETT 1968; LYON and MASON 1977; SILVER 1985). But our general conclusion that incompatibility between meiotic drive genes and their modifiers could give rise to hybrid sterility and that these genes are more likely to be on the *X* and *Y* chromosomes than on autosomes still stands.

CYTOPLASMIC SEX RATIO DISTORTERS AND HYBRID DISRUPTION

The inheritance of cytoplasmic genes is typically uniparental and more often than not exclusively maternal. As a consequence the male represents an evolutionary dead end for cytoplasmic genes, be they mitochondrial, viral, bacterial or whatever. In several groups of insects (UYENOYAMA and FELDMAN 1978; WERREN 1987; WERREN, NUR and WU 1988; HURST 1991) and plants (FRANK 1989) cytoplasmic genes are found which kill males or in hermaphrodites prevent androgenesis. By killing males the cytoplasmic genes advantage their clonal relatives in the surviving sisters of the dead males. This advantage might be due to a redirection of resources, reduced crowding or even a reduced probability of inbreeding.

We model the evolution of cytoplasmic male killers using similar equations to those of WERREN (1987). We assume that all eggs that inherit the cytoplasmic element die if they are male. Half the eggs that have not received the cytoplasmic element develop as uninfected males and half as uninfected females. The value β is the proportion of offspring that are female and carry cytoplasmic male killers. Females with infected cytoplasm suffer a reduction in fitness to W relative to uninfected females (Table 5A). Resources which are liberated by male killing are partially redirected toward other zygotes, or in the case of hermaphrodites, to female tissue. The net effect is that fertility declines, so W is usually less than one but greater than half. In a population with a 1:1 sex ratio, the condition for invasion of cytoplasmic male killers is approximately,

$$W\beta > \frac{1}{2}. \tag{8}$$

If transmission of the cytoplasmic element is complete ($\beta = 1$), invasion can lead to fixation of the cytoplasmic gene and population extinction due to the absence of males. Alternatively, polymorphism results at frequency,

$$t = \frac{(2W\beta - 1)}{(W\beta + W - 1)}. \tag{9}$$

Polymorphism will also result if W is negatively frequency dependent (WERREN 1987).

The most likely reason for negative frequency dependent selection is the appearance of nuclear suppressors of male killing. As the male-killer invades, the population sex ratio becomes increasingly female biased. The bias in the sex ratio, though selected at the cytoplasmic gene level, decreases the fitness of most nuclear genes. As a consequence, nuclear genes which neutralize the distorter cytoplasmic gene are favoured (WATSON 1960; WATSON and CASPARI 1960; UYENOYAMA and FELDMAN 1978; CHARLESWORTH and GANDERS 1979; WERREN 1987; TAYLOR 1990). Two types of suppression need to be considered. In the first, the maternal genotype causes a reduction in the transmission of the cytoplasmic element to eggs or a reduction in male killing activity, thereby pro-

TABLE 5

Fitness and transmission probabilities of cytoplasmic elements

(A) Without nuclear suppressors						
Female cytoplasm	Not infected		Infected			
Frequency	$1 - p$		p			
Fitness	1		W			
Zygote cytoplasmic	Not infected		Infected	Not infected		
Zygote sex	Male	Female	Female	Male	Female	
Zygote frequency	0.5	0.5	β	$(1 - \beta)/2$	$(1 - \beta)/2$	
(B) With nuclear suppressors						
Female cytoplasm	Not infected + suppressor		Infected + suppressor			
Frequency	$1 - p$		p			
Fitness	$1 - V$		$(1 - V)W^*$			
Zygote cytoplasm	Not infected		Infected		Not infected	
Zygote sex	Male	Female	Male	Female	Male	Female
Zygote frequency	0.5	0.5	$\beta(1 - \phi)$	$\phi\beta$	$(1 - \beta)/2$	$(1 - \beta)/2$

ducing a more normal sex ratio among offspring. In the second, the paternal genotype contributes to suppression as well. Following our previous discussion, we consider the conditions for the spread of active (costly) suppressors.

If the frequency of males in the population is p the reproductive value of each sex is given by Equation 5. These values depend on t, the proportion of infected females. If the value of t is steady, the population sex ratio is $(1 + t):(1 - t)$ and the reproductive values are approximately,

$$R_f = 1, \qquad R_m = \frac{1 + t}{1 - t}. \tag{10}$$

First consider maternal suppression. Let $1 - V$ be the cost of suppressing the activity of the cytoplasmic male killer. This cost is paid both by females carrying the infection and those that do not. The suppressor alters the transmission of the cytoplasmic element or reduces its male killing activity so that some infected sons survive. But this reduces the proportion of offspring that are female and carry cytoplasmic male killers by a fraction ϕ, where $\phi = 0.5$ is complete suppression and $\phi = 1$ is no suppression. The cost of redistributing resources from killed males is thereby reduced from W to W^*, where $W < W^*$. Under these assumptions (Table 5B), the maximum cost of an autosomal suppressor (V) that permits invasion can be derived by comparing the fitness of a female carrying the suppressor to one without the suppressor. This is most easily interpreted on the assumption that suppression is complete, $\phi = 0.5$, and therefore $W^* = 1$,

$$V < t[1 - W(1 - t\beta)]. \tag{11}$$

The maximum cost of suppressing the cytoplasmic elements activity is an increasing function of t, the proportion of females infected (Figure 2). This relationship holds for autosomal and X-linked suppressors, both in male and female heterogamety. Y-linked suppressors in female heterogamety are not expected to evolve as the Y chromosome has the same interest as the cytoplasmic elements because it is uniparentally inherited through females as well. If anything, the Y might carry enhancers.

The paternal genotype may also evolve means for controlling cytoplasmic elements. Male killing is particularly bad for sperm when there is multiple mating, because the redistribution of resources from killed males need not end up nourishing zygotes containing related genes. For simplicity we assume that females mate only once and that suppression is due to a dominant paternal gene. The fitness parameters are the same as with maternal suppressors, $1 - V$, ϕ, W^*, save that the suppressor function is introduced in the male ejaculate. Under these assumptions the maximum cost of an autosomal or X-linked suppressor that permits invasion is given by Equation 11. Selection for Y-linked suppressors when the male is the heterogametic sex is very similar (Figure 2),

$$V < t[1 - W(1 - \beta)]. \tag{12}$$

If the female is heterogametic, Y chromosomes always occur in females and so cannot carry genes for paternal suppression.

These relationships show that active (costly) suppressors of cytoplasmic disruption are increasingly likely to spread as the frequency of infected females increases. Their spread will stop the cytoplasmic element from going to fixation and causing extinction. On this argument nuclear genes for paternal and maternal suppression are likely to be equally common, unless there are mechanistic reasons why one type of suppression is more likely to evolve. We expect that

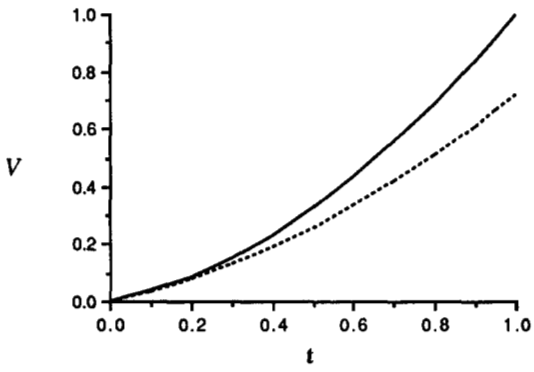

FIGURE 2.—The maximum cost (V) for invasion of a nuclear suppressor plotted against the frequency of female infection with a cytoplasmic male-killer (t). Maternal transmission of the cytoplasmic element occurs with frequency $\beta = 0.6$, which reduces female fitness to $W = 0.7$. Cost curves are shown for autosomal and X-linked suppressors (solid line) and for Y-linked suppressors (dotted line) when males are the heterogametic sex.

cytoplasmic elements and nuclear suppressors will coevolve in an antagonistic manner; the cytoplasm evolving new ways of evading suppression and causing female biased sex ratios, and the nuclear genes responding by evolving new mechanisms of stopping this activity. Presumably the nucleus has the upper hand, otherwise biased sex ratios would be much more common than they are.

In the new context of a hybrid, this nuclear control might breakdown. If both paternal and maternal effects are needed to tame cytoplasmic genes, hybrid crosses will cause a loss of control over cytoplasmic genes, allowing them to once more cause male disruption. We would expect that both directions of hybrid cross result in weakened control of the cytoplasm, though there may be asymmetries due to different contributions of maternal and paternal suppression. Full release will lead to male killing. Partial release might not cause death but result in lowered male viability. Male sterility might also occur if suppression protects the fertilized zygote but fails to protect the cytoplasmic elements acting when they detect male-specific gene activity in the male gonads.

Quick turnover of cytoplasmic sex ratio distorters and their suppressors has been experimentally investigated in a number of *Drosophila* species that harbor the cytoplasmic distorter called sex ratio (*SR*) which causes male-killing. MORIWAKI and KITAGAWA (1957) observed an initial increase in frequency of *SR* in a Japanese strain of *Drosophila bifasciata* held in population cages. Similarly MAGNI (1959), starting with equal proportions of infected and uninfected females of *Drosophila fasciata*, found a consistent decrease in the percentage of normal flies until only 10% remained. After several more generations this trend reversed. This pattern he attributed to evolutionary change in the cytoplasm and genotype concerned. IKEDA (1970) examining Japanese strains of the same species found persistence of *SR* for 2 years, though a consistent decline in *SR* females was seen in all experimental cages. FITZ-EARLE and SAKAGUCHI (1986) examining laboratory populations of *D. melanogaster* infected with the *SR* organism of *Drosophila nebulosa* observed variable changes in the frequency of females depending on the start conditions. Under some instances the frequency of females increased but not to fixation (and population extinction). But under most circumstances the frequency of females declined and then went through damped oscillations before settling to a 50:50 sex ratio. The involvement of nuclear genes in suppressing the expression of *SR* has been demonstrated in a number of systems (*Drosophila prosaltans*: CAVALCANTI, FALCAO and CASTRO 1957; *Drosophila willistoni*: MALOGOLOWKIN 1958; *Drosophila paulistorum*: MALOGOLOWKIN 1958).

Similar turnover has been reported in elements that cause cytoplasmic male sterility in plants (FRANK 1989). In numerous examples the cytoplasmic sterility gene remains in the population but is suppressed by nuclear genes (*e.g.*, *Phaseolus vulgaris*) (MACKENZIE 1991). There is also extensive evidence that hybrid male sterility in plants can be caused by the release from suppression of cytoplasmic male sterility factors (*e.g.*, *Thymus vulgaris*) (COUVET, BONNERMAISON and GOUYON 1986). Indeed about 20% of all cases of cytoplasmic male sterility have been discovered by their exposure and derepression in hybrids (FRANK 1989). This fact has been applied to emasculate hybrids of a number of crops (DUVICK 1959) and we see this as confirmation of our theoretical predictions.

A parallel effect could explain male sterility in the *D. paulistorum* complex. EHRMAN *et al.* (1989) have shown that in the *D. paulistorum* complex, sterility of hybrid males is due to the proliferation of vertically transmitted symbionts (staphylococci) within the testes. If the symbionts are tamed sex ratio distorting organisms let loose by the absence of genes which can suppress their activity then this system would fit to our pattern. The *D. paulistorum* complex is known to have active sex ratio distorting spiroplasmas (MALOGOLOWKIN and POULSON 1957). *Glossina* species produce sterile hybrid males, and one of the factors causing this sterility has been shown to be maternally inherited though no putative cytoplasmic gene has been identified (GOODING 1990).

Similar cytoplasmic genes are suspected to cause mortality of some Lepidoptera hybrids, though in this group the Y and cytoplasm function as a single linkage group. These instances are notable in that they go against Haldane's rule. The male killing reported in the moth *Pygaera pigra* in crosses between males from Berlin and females from Finland has been shown to be due to a a maternally inherited gene (FEDERLEY 1911, 1936). BOWDEN (1966) has reported a heavy

female bias in the sex ratio produced by hybrids between *Pieris napi* and *P. n. bryoniae*. All cases of bias occurred in *napi* male × *bryoniae* female crosses, giving hybrid males with *napi X*, *bryoniae Y* and *bryoniae* cytoplasm. The effect was believed to be maternally inherited implying that the cytoplasm could be the causative factor. In a later study of sex ratios of *P. napi*, BOWDEN (1987) found an excess of females and greater than 50% mortality, which are suggestive that cytoplasmic male killers are involved. In a few cases the genetics of male hybrid disruption have been investigated, and as predicted the sterility genes are maternally inherited (*e.g.*, *Heliothis*: LANSMAN, AVISE and HUETTAL 1983). The possibility of the *Y* imprinting the *X* while in the female cannot be ruled out as the cause of such effects (ROEHRDANZ 1990). However, the observation of cytoplasmic viruses in the testes of the sterile males is strongly supportive of our view (DEGRUGILLIER 1989).

Not all cytoplasmic sex ratio distorters act by forcing male mortality or sterility. The induction of thelytoky (parthenogenesis resulting in females) by cytoplasmic genes has been indicated in a number of species including wasps and coccids (HURST, GODFRAY and HARVEY 1990). The most complete report is that of thelytoky in the parasitoid wasp, Trichogramma (STOUTHAMER, LUCK and HAMILTON 1990). It is perhaps significant that the hybridization of various species of arrhenotokous (sexual) Trichogrammids often results in females which reproduce thelytokously (NAGARKATTI 1970; NAGARKATTI and FAZALUDDIN 1973; PINTEREAU and BABAULT 1981).

Certain Isopod and Amphipod crustaceans have been shown to harbour cytoplasmic genes (bacteria or microsporidia) which have the ability to override nuclear sex determination. Hence presumptive males (*XY*) can become female when infected (JUCHAULT and LEGRAND 1989; LEGRAND, LEGRAND-HAMELIN and JUCHAULT 1987). Nuclear genes (*M* factors) which suppress this activity have been demonstrated (LEGRAND, LEGRAND-HAMELIN and JUCHAULT 1987). It is certainly conceivable that upon hybridization the suppressor function is lost and that all female broods result. There is however a sparsity of information on isopod and amphipod hybrids and thus the validity of our suggestion is hard to assess in these groups.

DISCUSSION

The explanation for Haldane's rule presented here, and independently put forward by FRANK (1991), stands in contrast to that proposed by CHARLESWORTH, COYNE and BARTON (1987) and COYNE and ORR (1989). They argue that the phenomenon is explained by the faster evolution of sex chromosomes. In particular, advantageous recessive and underdominant genes will evolve more rapidly on the *X* chromosome than on autosomes. This is because genes on the *X* chromosome are hemizygous in the heterogametic sex, so advantageous recessives will be phenotypically expressed and immediately favored by selection. On autosomes such genes will not be favored until they reach sufficiently high frequency for homozygotes to appear. This deduction may explain Haldane's rule if the contribution of a gene to sterility in hybrid crosses is proportional to the rate of divergence of genes due to the substitution of advantageous recessives.

There are difficulties with this theory. First, CHARLESWORTH, COYNE and BARTON (1987) suggest no clear reason or possible mechanism why the faster accumulation of advantageous recessives on *X* chromosomes results in hybrid sterility, inviability or absence. There seems no obvious reason for this to be the case. A prime advantage of the meiotic drive hypothesis is that it deals with a system whose normal function is the destruction of competitor chromosomes and gametes that can easily lead to reduced fertility. Further the advantageous recessive theory fails to explain why there is no greater contribution of the *X* chromosome to morphological or behavioral differences between species (CHARLESWORTH, COYNE and BARTON 1987; COYNE and ORR 1989). The genes for such traits are found on all chromosomes. From our perspective genes for sterility are simply different from those for morphological or behavioral traits.

Second, if the mechanism of infertility was based simply on the amount of genetic change then the hypothesis is highly questionable. Though it is true that the accumulation of advantageous recessives will be faster on the *X*, it will also be the case that mildly deleterious recessives accumulate more quickly on autosomes. This follows from precisely the same logic as CHARLESWORTH, COYNE and BARTON apply: deleterious recessives on the *X* are expressed in the heterogametic sex and immediately selected against, whereas on autosomes they will remain hidden until they become homozygous (CHARLESWORTH, COYNE and BARTON 1987). On the assumption that neutral or nearly neutral mutants are the major factor contributing to molecular evolution we would expect that autosomes will change more quickly than the *X*.

However, there is a further complication to consider. MIYATA *et al.* (1987) have suggested that because of the far greater number of cell divisions in spermatogenesis than oogenesis males serve as the mutation generators in molecular evolution. As a consequence *X* chromosomes, which spend only a third of their time in males, will have a lower rate of molecular evolution than autosomes, which spend half of their time in males. This prediction is borne out for both silent and replacement sites in a comparison of 41 genes in human and mouse (MIYATA *et al.* 1987,

1990). Thus if genetic distance is the cause of hybrid sterility then we would predict that the loci for sterility should predominantly map to the autosomes. In stating this we assume, as is commonly done, that the frequency of mutations causing deleterious recessives is higher than the frequency of mutations causing advantageous recessives.

More immediate practical problems with CHARLESWORTH, COYNE and BARTON's hypothesis emerge on examination of the some of the rare, "exceptional" males in hybrid Drosophila crosses which are fully viable. In crosses between *D. melanogaster* and *Drosophila sechellia*, about 1 in 2000 males are *XO*, resulting from the fertilization of nullo-*X* eggs with *X* sperm. Unlike the *XY* males which die at the third instar, these *XO* males survive through to adulthood (HUTTER 1990). CHARLESWORTH, COYNE and BARTON's hypothesis assumes that the *Y* is silent and predicts that it is more or less irrelevant to hybrid disruption, though the hypothesis is ambiguous on this point. Conversely, the drive hypothesis predicts that the *Y* is important as the principal suppressor of *X* drive and thus its removal should aid survival, which is exactly what is observed.

Theoretical objections to CHARLESWORTH, COYNE and BARTON's notion are one thing, practical demonstration of the validity of their or our hypothesis is another. If a novel meiotic drive agent that alters the sex ratio is found in a natural or laboratory population then the drive theory is amenable to testing. If modifiers that control the drive element and stabilize the sex ratio subsequently appear in the population, then these stocks can be backcrossed to stocks (same or related species) lacking this drive system. If Haldane's rule is obeyed and it is possible to identify the loci responsible for the effect, we predict that the meiotic drive locus will also be involved in sterility. Any meiotic drive gene with activity in only one sex could be a cause of hybrid sterility in that sex. We predict that most of the time these genes will be on the *X* and *Y* chromosomes. But additionally, autosomal meiotic drivers with sex specific activity will have the same effect. GOLIC (1990) has shown that an incompatibility between *SD* genes and modifiers gives rise to hybrid male sterility in certain crosses. *SD* has male specific activity. Similarly SANO (1990) has demonstrated that male sterility in rice hybrids is due to a meiotic drive gene (pollen killer) with male specific activity. A strong case for the involvement of meiotic drive genes in hybrid sterility between species comes from *Mus domesticus* × *Mus musculus* crosses. One gene controlling hybrid sterility maps to chromosome *17*, 6 cM distally from the *T* locus (FOREJT and IVANYI 1975). We suspect that this gene is involved in the *t* drive system. In the instances above the drive genes are autosomal but their expression is specific to the heterogametic sex, and this is the typical pattern for autosomal drive. The only exception to this rule that we know of is that of chromosome *1* drive in female mice (AGULNIK, AGULNIK and RUVINSKY 1990). The reason for this association is not known.

The taxa in which sex chromosome meiotic drive has been reported (Table 1) are also the main ones which have been shown to obey Haldane's rule (*i.e.*, Aves, Mammalia, Lepidoptera and Diptera), with the exception of one fish example. Those which do not consistently obey Haldane's rule have not been shown to have problems with sex chromosome drive. The list was constructed with no bias toward investigating cases of meiotic drive only in those groups which obey Haldane's rule and it is for that reason that we comment on this finding. These groups fall into two subdivisions: those with female heterogamety (Aves and Lepidoptera) and those with male heterogamety (Mammalia and Diptera). The latter are also distinguished by having centromeric pairing at meiosis (DARLINGTON 1939). Heterogametic females are particularly vulnerable to drive because of the ease with which drive can be accomplished; that is, the drive chromosome has simply to orient the correct way on the meiotic plate to prevent being cast into the polar body. The association with centromeric pairing may also be significant. Maybe this is a precondition for drive to occur in organisms with male heterogamety. There is not space here to consider why this is the case. Nonetheless we suspect that Haldane's rule is not a universally applicable relationship but is restricted to those groups in which meiotic drive is a problem. Thus we predict that if in the future any taxa are shown to have features predisposing them to meiotic drive they will also obey Haldane's rule.

Our model considers hybrid disruption as being due to an incompatibility between sex ratio distorters in general, of which *X-Y* meiotic drive is but one subset. The second main class we consider are cytoplasmic sex ratio distorters. These distorters are known to force a female bias to the sex ratio, often by killing males (review, HURST 1991), feminizing them (BULL 1983; LEGRAND, LEGRAND-HAMELIN and JUCHAULT 1987) or causing parthenogenesis (HURST, GODFRAY and HARVEY 1990). This is advantageous to the selfish genetic elements because cytoplasm is nearly always uniparentally inherited through the female line. By killing males, the cytoplasmic genes redirect resources to their clonal relatives in female offspring.

As with drive elements, suppressors are likely to evolve that control distortion by cytoplasmic genes. These suppressors will be located in the nucleus. Nuclear genes gain from suppressing the action of male-killers for two reasons. First, because male-killing usually reduces fertility. Second, because producing a

female biased sex ratio is generally disadvantageous, particularly if the male killer has spread and causes a female biased sex ratio in the population. Suppressors are favored on all chromosomes except the *Y* in female heterogametic species, where the *Y* chromosome has the same interests as the cytoplasm and, if anything, might carry enhancers. Suppression is favored in both female and male genotypes.

We expect that cytoplasmic elements and nuclear suppressors will coevolve in an antagonistic manner; the cytoplasm evolving new ways of evading suppression and nuclear genes evolving new mechanisms for stopping this activity. If cytoplasmic distorters are usually tamed within a species it is likely that when in the novel environment of a hybrid they will be released. This will cause unisexual hybrid male disruption regardless of heterogamety. As both maternal and paternal suppression is selected for, both directions of hybrid cross could result in weakened control of the cytoplasm, asymmetries reflecting the relative contributions of male and female genotypes. Full release will lead to male killing and partial release to lowered viability. Sterility might also occur if cytoplasmic release from suppression is triggered by the male-specific gene activity in the male gonads. Neither the meiotic drive nor the advantageous recessive models predict male only disruption.

Within the Lepidoptera the direction of sex specific disruption is sometimes dependent on the direction of the cross. That is if species 1 is the father and species 2 the mother, the cross is pro-Haldane female sterile, but the reciprocal is anti-Haldane male sterile (AE 1964; J. W. HARRISON reviewed in COCKAYNE 1938). This is compatible with a model incorporating both cytoplasmic effects and *X* drive. If species 1 harbors cytoplasmic distorters the males will be disrupted in crosses between females of species 1 and males of species 2; and if species 1 has *X*-drive or species 2 has *Y*-drive then the female offspring of the reciprocal cross will be disrupted. It is not at all clear that any other suggested explanation of sex specific hybrid disruption can account for these and other similar patterns.

We do not presume to claim that every instance of unisexual hybrid disruption is due to an incompatibility between diverged sex ratio distorter systems, be they meiotic drivers or cytoplasmic distorters. Neither do we rule out effects due to the spread of advantageous recessives as suggested by CHARLESWORTH, COYNE and BARTON (1987). As we do not know what sort of effect advantageous recessives have in hybrid crosses, we cannot discount this as a possible mechanism. But we hope that the theory and supporting evidence that we have presented here stimulates attempts to test the sex ratio distorter hypothesis and reassess previous explanations of unisexual hybrid disruption.

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