EXPERIMENTAL AND THEORETICAL ANALYSIS OF THE "SEX-RATIO" POLYMORPHISM IN *DROSOPHILA PSEUDOOBSCURA**

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ABSTRACT

The Sex-ratio chromosome (SR) is a widespread, multiply inverted rearrangement of the *X* chromosome present in several species of Drosophila. Male carriers transmit mostly *X*-bearing sperm. In the absence of strong counteracting selection, SR is expected to increase rapidly to fixation, causing extinction. The present study incorporates a selection-components analysis of SR in laboratory populations, using the closely linked Esterase-5 locus as a marker. Estimated fitnesses show directional viability selection against SR in both males and females, heterosis for fertility and no significant effects on virility, the male adult component of fitness. Estimated fitnesses satisfy conditions for protected polymorphism and accurately predict gene-frequency trajectories in experimental populations. A model of SR gene-frequency evolution is developed, which incorporates sex-linkage, meiotic drive, viability, fertility and virility selecton. We show that conditions for protected polymorphisms are not unduly restrictive and that differential fitness among males is not sufficient for protected polymorphism, irrespective of the degree of meiotic drive.

IT is widely believed that the most common mode of chromosomal sex determination involves equal representation of *X* and *Y* chromosomes among gametes of the heterogametic sex, leading to equal proportions of males and females among progeny. Here we study a widespread case of non-Mendelian transmission of sex chromosomes in Drosophila, and report experimental and theoretical results that may explain the operation of natural selection on such variants.

Several species of Drosophila exhibit a naturally occurring condition known as "Sex-ratio" (SR). Males hemizygous for an *X* chromosome bearing the SR gene (or genes) produce mostly (90–100%) female progeny. The condition is sex-limited in expression and is transmitted as a single *X*-linked factor. SR-bearing chromosomes are cytologically distinguishable due to their association with inversions relative to Standard (ST) *X* chromosomes (STURTEVANT and DOBZHANSKY 1936; DOBZHANSKY and SOCOLOV 1939; JUNGEN 1968; MILLER 1971). In *D. pseudoobscura*, the SR-bearing chromosome is characterized by three non-

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overlapping inversions in complete coupling linkage disequilibrium (DOBZHANSKY 1939; WALLACE 1948). The distorted sex ratio among progeny of SR males is due to prezygotic effects, now known to include degeneration of *Y*-bearing spermatids during spermiogenesis (POLICANSKY and ELLISON 1970; HAUSCHTECK-JUNGEN and MAURER 1976). Following SANDLER and NOVITSKI (1957), we use the term "meiotic drive" to denote distortion of the ratio of sex chromosomes among gametes of SR males, irrespective of the operation of other modes of selection, such as differential mating success of SR and ST males.

The SR condition has been reported in both palearctic and nearctic members of the *obscura* group, including *D. affinis*, *obscura*, *subobscura*, *algonquin*, *pseudoobscura*, *persimilis*, *athabasca*, *azteca* and perhaps *bifasciata* (MORGAN, BRIDGES and STURTEVANT 1925; GERSHENSON 1928; STURTEVANT and DOBZHANSKY 1936; NOVITSKI 1947; BUZZATI-TRAVERSO and SCOSSIROLI 1955; JUNGEN 1967). An apparently homologous condition occurs in *D. paramelanica*, a member of the closely related *melanica* group (STALKER 1961). In *D. pseudoobscura*, all populations sampled in the American Southwest contain some SR-bearing chromosomes, usually at frequencies of 5 to 15% (DOBZHANSKY and EPLING 1944). Frequencies of SR reach a maximum of 30% in southern Arizona and northern Mexico, but decline in the northern part of the species range (STURTEVANT and DOBZHANSKY 1936). Aside from seasonal fluctuations in some localities (DOBZHANSKY 1943), the clinal pattern of variation and local gene frequencies have been observed to remain relatively constant over several decades (DOBZHANSKY 1958). Thus, the SR condition is a long-standing feature of the genome, rather than a recent mutational event.

The persistence of the SR polymorphism must result from a balance between the forces of meiotic drive and counteracting selection, since, in the absence of some strong form of nongametic selection against SR, the driven chromosome is expected to increase rapidly to fixation (GERSHENSON 1928; EDWARDS 1961; HAMILTON 1967; WALLACE 1968). Extinction of the species would follow; the few male progeny of SR males are usually sterile (DARLINGTON and DOBZHANSKY 1942), and parthenogenesis is absent in these species.

Several modes of selection could account for the failure of SR to increase in natural populations. Suppressors of SR meiotic drive have been reported in *D. affinis* and *paramelanica* (NOVITSKI 1947; STALKER 1961; VOELKER 1972), but there is no evidence of comparable modifying systems in *D. pseudoobscura* (POLICANSKY and DEMPSEY 1978; CURTSINGER 1978). Viability and fertility selection against SR-bearing individuals could lead to stable polymorphism if the relative fitnesses were to satisfy specifiable conditions (EDWARDS 1961; THOMSON and FELDMAN 1975). WALLACE (1948) measured relative viability, fertility, longevity, fecundity and sexual activity in laboratory populations of *D. pseudoobscura* and found strong viability and fertility selection against SR homozygous females. The observed selection was judged to be sufficient for polymorphism, but there remained several difficulties with this interpretation. Because of the lack of replicated fitness estimation experiments, it is not possible to assess the statistical significance of differences between genotypes; adult com-

ponents of fitness are usually associated with large variance. In a reconsideration of WALLACE's data, EDWARDS (1961) found that estimated fitnesses inserted into a specific model produced model trajectories that differed from those observed in population cages. WALLACE (1968) later argued that conditions for stable polymorphism, which enable meiotic drive to be balanced by viability and fertility selection, are too restrictive to provide a robust explanation for the persistence of the polymorphism. He offered a "group" selection alternative: SR frequently increases and leads to extinction of local populations, which are recolonized by individuals from populations having low frequencies of SR. With sufficiently high rates of local extinction, such a means of selection between groups may prevent fixation of SR in the overall population, perhaps in a manner analogous to the interdeme selection scheme proposed by LEWONTIN (1962) for the *t*-allele system in Mus. Recently, POLICANSKY (1974, 1979) proposed that reduced sperm production by SR males causes decreased fertility or mating success relative to ST males and that, as a result, there may be not net force tending to increase the frequency of SR in populations. Subsequent experiments by BECKENBACH (1978) have not verified the unconditional fertility reduction of SR males.

Clearly, there is no agreement on the manner in which selection operates to balance SR meiotic drive. We propose a parameterization of the operation of natural selection as shown in Table 1, where "X_r" denotes the SR-bearing chromosome. Following PROUT (1971), "virility" is defined as the male adult component of fitness. Using that mode of quantification of the problem, estimates of larval and adult components of fitness in laboratory populations of *D. pseudoobscura*, as well as measurements of sexual selection in the field, are presented. The experimental studies utilize a selection-components analysis design and an electrophoretic marker for the SR chromosome. The equilibrium analysis of a general model of SR evolution is also presented. It will be shown that the group-selection hypothesis is unnecessary, in the sense that conditions for stable polymorphism with some other modes of selection are not particularly restrictive. We also demonstrate that differential fitness among males is not sufficient for stable polymorphism at a sex-linked locus, irrespective of the degree of meiotic drive.

TABLE 1

Parameterization of the operation of natural selection on SR

	Genotypes				
	XX	X_rX	X_rX_r	XY	X_rY
Viability	a	h	b	c	d
Fertility	f_1	f_2	f_3	—	—
Virility	—	—	—	v_1	v_2
Frequency	U	V	W	X	Y

"X_r" denotes the SR-bearing X chromosome.

EXPERIMENTAL DESIGN

The selection-components analysis is derived from the experimental designs of PROUT (1969, 1971) and ANDERSON and WATANABE (1974). Referring to the fitness parameters in Table 1, let $h = v_1 = f_2 = 1$, without loss of generality, leaving seven independent parameters to be estimated. The experimental procedure involves observation of a series of one-generation transitions in which the mixture of parental genotypes is controlled. Observation of the resulting progeny types yields an estimate of one fitness component. The necessary parental mixtures are shown in Table 2.

Viability estimation is straightforward. Heterozygous females, in which segregation is normal, are mass-mated to one type of male. The relative viabilities of the resulting progeny types are those factors by which observed progeny genotype frequencies must be weighted to fit Mendelian expectations. With sex-linked loci, there is no single type of cross that yields all possible genotypes among progeny; consequently, viability estimation must be performed in several parts. Preliminary experiments showed that females develop much more rapidly than males; hence, sampling progeny of Viability Cross I without regard to sex would result in artificially low estimates of the parameters c and d. Sampling was therefore performed independently for males and females in Viability Cross I. Viability differences between the sexes were estimated independently in Cross III. Note that the fitness estimates are obtained in the absence of one or more genotypes among the progeny. It will be shown that there are internal checks for consistency of the viability estimates and their sensitivity to the presence of all genotypes among the progeny.

Three types of crosses are necessary for virility estimation. Mixtures of SR and ST adult males are allowed to compete for mates of only one genotype. Using

TABLE 2

Mixtures of parental genotypes used in the selection-components-analysis

Cross		Parental mixture XX	X_rX	X_rX_r	XY	X_rY	Estimates obtained
Viability	I	—	1	—	1	—	a/h, d/c
	II	—	1	—	—	1	b/h
	III	1	—	—	1	—	a/c
Virility	I	1	—	—	q_1	q_2	v_2/v_1
	II	—	1	—	q_1	q_2	v_2/v_1
	III	—	—	1	q_1	q_2	v_2/v_1
Fertility	I	p_1	p_2	—	1	—	f_1/f_2
	II	p_1	p_2	—	—	1	f_1/f_2
	III	—	p_2	p_3	1	—	f_3/f_2
	IV	—	p_2	p_3	—	1	f_3/f_2

Observation of genotype frequencies among the resulting progeny of each cross yields one estimate of the indicated fitness parameter(s) per replicate.

the observed genotype frequencies among resulting adult progeny and previous viability estimates, it is possible to estimate the relative virility of the paternal genotypes. The sterility of male progeny of SR males justifies the assumption of complete meiotic drive for the following calculations; slight variations in the degree of drive have negligible effect on the virility estimates (and no effect on viability and fertility estimates). As an illustration, consider the analysis of data from Virility Cross I; other crosses are similar. All female parents are XX, while ST and SR male parents are present in relative frequencies q_1 and q_2, respectively. The progeny genotypes XX and X_rX are expected in the proportions $v_1q_1/2\bar{V}$ and $v_2q_2/\bar{V}$, respectively, among female zygotes, where $\bar{V} = v_1q_1/2 + v_2q_2$. Let P_1^* and P_2^* represent the observed proportions of XX and X_rX adult progeny after viability selection. Then $P_1^* = v_1q_1a/2\bar{V}\bar{L}$ and $P_2^* = v_2q_2h/\bar{V}\bar{L}$, where $\bar{L} = (v_1q_1a/2 + v_2q_2h)/\bar{V}$. Thus, $v_2/v_1 = P_2^*q_1a/2P_1^*q_2h$. The parameters a and h are known from previous viability estimation experiments, q_1 and q_2 are known without error, and P_1^* and P_2^* are measured for each replicate. Thus, each replicate mixture of parental genotypes yields one estimate of the relative virility of SR and ST males. By varying the mixture of SR and ST males among parents of the virility crosses, it is possible to detect frequency-dependent virility. Further, comparison of the virility estimates over the three types of crosses, I to III, yields an estimate of mating interaction.

It is well known that, even under apparently uniform conditions, laboratory cultures of Drosophila can exhibit microhabitat heterogeneity and that mate selection by females can be strongly influenced by the origin of the males. In order to control these effects on the virility estimation experiments, mixtures of male parents were derived from only one culture per replicate, rather than from mixing known numbers of SR males from one culture and ST males from another.

For the estimation of relative fertilities, mixtures of two female genotypes were used in the four types of fertility crosses, giving estimates of f_1 relative to f_2, and f_3 relative to f_2. As an illustration, consider the estimation of the relative fertility of XX and X_rX females from Fertility Cross I; analysis of the other crosses is similar. The two types of females are present among parents in the proportions p_1 and p_2, respectively, while all males are XY. The resulting female zygotes XX and X_rX are expected in proportions $(p_1f_1 + p_2f_2/2)/\bar{F}$ and $p_2f_2/2\bar{F}$, where $\bar{F} = p_1f_1 + p_2f_2$. After viability selection, observed adults are expected in the proportions $a(p_1f_1 + p_2f_2/2)/\bar{F}\bar{L}$ and $hp_2f_2/2\bar{F}\bar{L}$, where $\bar{L} = (p_1f_1a + p_2f_2a/2 + p_2f_2h/2)/\bar{F}$. Denoting observed progeny genotypes XX and X_rX by P_1^* and P_2^*, some rearrangement gives $f_1/f_2 = p_2(P_1^*h - P_2^*a)/2p_1P_2^*a$. P_1^* and P_2^* are determined for each replicate, p_1 and p_2 are known without error, and a and h are known from the viability estimation experiments. Each replicate thus yields one estimate of f_1 relative to f_2. As in the virility data, it is possible to detect frequency-dependent effects by varying the mixture of maternal genotypes. Mating interaction can be detected by comparison of estimates of f_1 in Fertility Crosses I and II, and by comparison of estimates of f_3 in Fertility Crosses III and IV.

There is a basic logistic problem in measuring genotype frequencies among many test progeny. Previous work with SR has depended on either examination of larval salivary gland chromosomes or breeding tests to determine genotypes. These methods are particularly inefficient for measuring genotype frequencies in a mixture of unknown adult females; several larval progeny of each female must be examined (or reared and mated), since each carries only one maternal *X* chromosome. We have solved this logistic problem by using a polymorphic enzyme locus closely linked to SR as a marker. The technique allows direct determination of genotypes of male and female adults without the error inherent in sampling progeny.

In addition to the fitness estimation experiments, a series of long-term discrete generation populations has been maintained and sampled each generation in order to observe gene frequency trajectories. Data from these populations allow tests of the predictive value of the fitness estimates.

Because it is not possible to collect larvae of *D. pseudoobscura* in the field or to determine the age of wild-caught adults, viability and fertility estimates cannot be obtained from field collections. It is possible, however, to estimate sexual selection in the field by simultaneously measuring the frequency of SR among adult males and the frequency of females inseminated by SR males. Difference between these two measures indicates differential success of SR and ST males at obtaining mates, *i.e.*, sexual selection. It is implicitly assumed that the males collected are a representative sample of potential mates in the population.

MATERIALS AND METHODS

Origin and maintenance of stocks: All experimental stocks of *D. pseudoobscura* were collected at bait traps near the edge of an oak woodland in Jasper Ridge Biological Preserve, San Mateo County, California. SR averaged 4% among males at this site over a three-year period. SR stocks produced an average of 98% females in the laboratory. All SR stocks were examined for the presence of the characteristic inversions on the right arm of the *X* chromosome to insure that the SR arrangement was present.

Standardized stocks for species identification and determination of electrophoretic alleles were obtained from R. LEWONTIN, TIMOTHY PROUT, WYATT ANDERSON and FRANCISCO AYALA. Stocks were maintained at room temperature (approximately 21°) on Carolina Instant Medium seeded with live baker's yeast in either 8-dram shell vials or half-pint milk bottles. A 21-day discrete generation schedule was employed for routine stock maintenance. SR stocks were maintained through aunt-nephew crosses, each independently originating SR line being separately cultured.

Biochemical marker for SR: PRAKASH (1974) and POLICANSKY and ZOUROS (1977) have reported significant linkage disequilibrium between the SR inversions and the *1.04* allele of Esterase-5 (*Est-5*) suggesting the use of *Est-5* as a marker for SR. Linkage tests were performed by crossing SR *Est-5*$^{1.04}$/ST *Est-5*$^{.97}$ females with ST males and recording the *Est-5* genotype and sex ratio from male progeny. No recombinants were observed among 240 males tested. The upper 95% confidence limit on the recombination fraction is 1.5%. In fact, the esterase marker has been used in our routine stock maintenance for several years, and no recombinants have ever been observed. All 38 independently derived SR chromosomes from Jasper Ridge carry the *Est-5*$^{1.04}$ allele. There are four other common alleles of *Est-5* in the population.

Electrophoresis: Vertical slab-gel polyacrylamide electrophoresis was performed on a tris-borate continuous buffer system at pH 8.9. Sample preparation, running time and staining

procedures are as described by HUBBY and LEWONTIN (1966), with the exception that incubation in boric acid before staining was omitted.

Selection components analysis: All stocks used in the selection components analysis were derived from collections at Jasper Ridge. These included 12 independently isolated SR lines and 94 ST lines, each typed for Esterase-5. All stocks had been in the laboratory for at least six months before beginning the fitness estimation, and were maintained as isofemale lines.

Three generations of crosses were performed to generate parents for the selection components analysis. Random mixtures of the SR and ST lines were mass-mated in half-pint bottles. F_1 progeny were then pair-mated and scored for *Est-5* genotype. Mass-matings of known F_2 genotypes were then set up, the genotypes being chosen so that each culture would produce one of the mixtures of male or female genotypes shown in Table 2. This procedure avoids using the inbred SR lines directly in the generation of experimental stocks. Care was taken in the choice of F_2 genotypes to insure that parental mixtures for experiments would show a wide range of SR frequencies to facilitate the detection of frequency-dependent selection.

The experimental crosses were performed at room temperature in half-pint bottles with 60 males and 60 females per replicate. All parents were four- or five-day-old virgins at the commencement of the experimental crosses. Males and females were left together for four days and then scored for *Est-5* genotype. Mortality among parents before determination of genotype frequencies was negligible.

Preliminary experiments showed no evidence of genotype-specific differences in developmental rates within sexes. Except for Viability Cross III, 100 test progeny were collected on the second and third days after first emergence for females, up to the fifth day for males, and then scored for *Est-5* genotype. In Viability Cross III, all progeny emerging were collected and scored by sex for fifteen days after the first emergence. Only female progeny were sampled in Virility Crosses I and III and all fertility crosses.

Longterm populations: Ten discrete-generation populations were maintained in half-pint bottles under conditions identical to those for the fitness estimation experiments. Founding stocks were generated as above, with the initial populations enriched for SR, consisting of 5 XX, 25 X_rX, 30 X_rX_r, 18 XY and 42 X_rY, giving equal gene frequencies in the sexes. Each generation, 120 of the approximately 400 total adult progeny were randomly chosen, without regard to sex, as parents for the next generation. These were allowed to mate and lay eggs for four days; forty males and forty females were then sampled and analyzed for *Est-5* genotype. Regular sampling of the populations continued for twelve generations.

Sexual selection in the field: The frequency of SR among adult males collected at Jasper Ridge was estimated eight times over a 26-month period by mating wild-caught males with laboratory reared virgins and scoring broods consisting of 90% or more female progeny. Brood sex ratios clearly fall into two classes, normal and characteristically aberrant under the influence of SR (CURTSINGER 1978). The frequency of females inseminated by SR males was estimated by establishing isofemales lines and scoring broods consisting of 90% or more female progeny. Multiple insemination is common in some populations (ANDERSON 1974; COBBS 1977). Among the twenty iso-female lines that showed evidence of insemination by an SR male, none of the few male progeny were fertile, suggesting a lack of multiple insemination or complete sperm displacement. However, sperm mixing could result in fewer than 90% female progeny, even if one of the paternal genotypes had been X_rY; therefore, the methods employed here underestimate the success of SR males at obtaining mates.

RESULTS

Experimental

Results of the viability estimation experiments are shown in Table 3. Statistical tests have been made using the log-likelihood-ratio G statistic, which is approximately chi-square; it has advantages when partitioning is of interest

TABLE 3

Summary of progeny observed in Viability Crosses I to III

Cross	Reps	Estimator	Viability experiments Total progeny XX	X_rX	X_rX_r	XY	X_rY	N	Estimator mean
I	12	a/h	665	536	—	—	—	1201	1.24
I	12	d/c	—	—	—	704	495	1199	0.70
II	12	b/h	—	784	424	—	—	1208	0.54
III	126	a/c	4093	—	—	3389	—	7482	1.21

Cross	Estimator	G statistics G_h(df)	G_p(df)	G_t(df)
I	a/h	7.95 (11)	13.88 (1)**	21.83 (12)*
I	d/c	16.46 (11)	34.69 (1)**	51.15 (12)**
II	b/h	19.58 (11)*	122.8 (1)**	142.4 (12)**
III	a/c	183.9 (125)**	79.01 (1)**	263.0 (126)**

* Significant at 5% level; ** Significant at 1% level.
$G_p \equiv$ pooled fit to expected 1:1 genotype ratios; $G_h \equiv$ heterogeneity G between replicates; $G_t \equiv$ total G.

(FIENBERG 1977, pp. 48–52). There is consistent directional selection against SR in both males and females. In all twelve replicates of Viability Cross I, SR males show lower egg-to-adult survival than ST males, while in 11 of 12 replicates heterozygous females exhibit lower viability than ST homozygous females. In Viability Cross II, SR homozygotes show lower viability than heterozygotes over all replicates. Viability differences between genotypes are in all cases statistically significant.

Results of the virility estimation experiments are shown in Table 4. There is

TABLE 4

Summary of progeny observed in Virility Crosses I to III

Cross	Reps	Estimator	Virility experiments XX	X_rX	X_rX_r	N	Mean v_2/v_1
I	12	v_2/v_1	546	654	—	1200	0.97
II	12	v_2/v_1	312	640	245	1200	1.12
III	12	v_2/v_1	—	559	641	1200	1.02

Test	Source	Anova df	SS	MS	F
Mating interaction:	Among crosses	2	0.145	0.073	0.375(NS)*
	Within crosses	33	6.78	0.194	
	Total	35	6.93		
Frequency dependence:	Among groups	2	0.473	0.236	1.29 (NS)*
	Within groups	33	6.34	0.183	
	Total	35	6.87		

* NS means not significant at 5% level.
Among-cross variance indicates mating interaction; among-group variance indicates frequency dependent mating success. Groups are defined in the text.

no evidence of strongly reduced virility of SR males relative to ST males. Tests for mating interaction, made by comparing virility estimates over the crosses I to III, are not statistically significant. The data were therefore pooled and divided into three groups on the basis of high, intermediate or low frequency of SR males among parents. Analysis of variance on these grouped data indicates a slight tendency for increased virility of SR males when rare, but the overall analysis shows no statistically significant frequency-dependent virility. It is possible to test whether the pooled virility data conform to either of two hypotheses of interest, $v_2 = 0.5$, and $v_2 = 1.0$. Let Z_r represent the frequency of SR chromosomes from male parents among female zygotes, and let q_2 represent the frequency of SR among male parents. Then, setting, $v_1 = 1$,

$$Z_r = \frac{2v_2q_2}{2v_2q_2 + 1 - q_2} .$$

Z_r can be estimated from each virility cross replicate by weighting observed progeny frequencies by the relative viabilities; q_2 is known exactly for each replicate. Predicted curves of Z_r *vs.* q_2 for the two cases $v_2 = 0.5$, 1.0 are shown in Figure 1. Replicated goodness-of-fit tests using the G statistic indicate significant heterogeneity over replicates ($G = 558.66$, $p < 0.001$) and significant departure from expectations based on the hypothesis $v_2 = 0.5$ ($G = 267.52$,

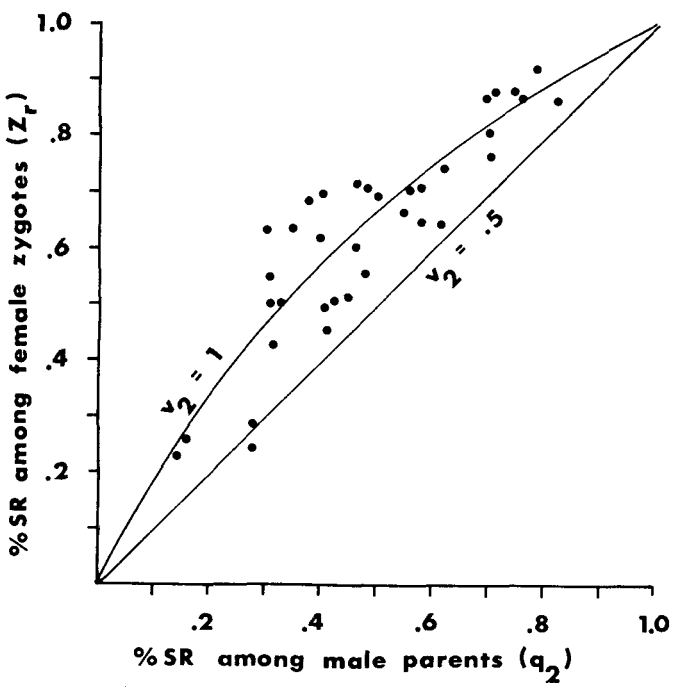

FIGURE 1.—Pooled data from the 36 replicates of Virility Crosses I to III. Expected curves for $v_2 = 0.5$ and $v_2 = 1.0$ are shown. Each estimate of Z_r is based on a sample of 100 progeny; q_2 is known without error for each replicate.

$p < 0.001$). The pooled data do not differ significantly from expectations based on the extrinsic hypothesis $v_2 = v_1 = 1$ ($G = 3.13$, $0.05 < p < 0.10$). Thus, in spite of the usual large variance associated with adult components of fitness, it is possible to reject the hypothesis that reduced virility of SR males even approximately balances SR meiotic drive.

Further information can be obtained from the virility data. First, the data from Virility Cross II allow an internal check for 1:1 segregation in females. The female progeny of heterozygous females are expected to be half homozygotes and half heterozygotes at fertilization, regardless of mate genotype or differential virility of males. Observed genotype frequencies among adult progeny can be used to estimate frequencies among zygotes by weighting by relative viabilities; the estimated ratio of homozygotes to heterozygotes among female zygotes is

$$[(P_1^*/a) + (P_3^*/b)]/(P_2^*/h)$$

where P_1^*, P_2^* and P_3^* represent observed XX, X_rX, and X_rX_r adult progeny. The expectation of the above value is 1.0; observed values did not differ significantly from 1.0 (mean $= 0.93$, $t = 1.05$, $p > 0.2$). A further check for internal consistency is possible using the Virility Cross II data. The parental mixture of genotypes was chosen in such a way that progeny of matings with XY and X_rY males could be distinguished (ST chromosomes in females differ from ST chromosomes in males at the *Est-5* locus). Since segregation is normal in heterozygous females, matings with ST males are expected to result in equal proportions of XX and X_rX genotypes among female zygotes. Observed adult progeny of ST males show departure from equal frequency because of viability differences between the genotypes. The departure from equality gives an independent estimate of the relative viability of XX and X_rX genotypes. The viability estimate obtained from these virility data does not differ significantly from previous estimates obtained in Viability Cross I (mean $a/h = 1.42$, $t = 0.81$, $p > 0.4$). Similar analyses of the progeny of matings with SR males give an estimate of the viability parameter b, which does not differ significantly from that obtained in Viability Cross II (mean $b/h = 0.62$, $t = 1.30$, $p > 0.2$). Among progeny males, the genotypes XY and X_rY are expected in equal frequencies among zygotes. The observed ratio among adult progeny gives an estimate of the viability parameter d, which does not differ significantly from that obtained in Viability Cross I (mean $d/c = 0.78$, $t = 1.32$, $p > 0.2$). These tests demonstrate that estimates of relative viability obtained in the absence of one or more genotypes, as in Viability Crosses I and II, do not change significantly when all possible genotypes are present among the progeny.

Results of the fertility estimation experiments are shown in Table 5. There is a fairly consistent pattern of heterosis, in that f_2 equalled or exceeded f_1 and f_3 in 17 and 20 of 24 replicates, respectively. Genotype differences in fertility are statistically significant (mean $f_1/f_2 = 0.865$, $t = 1.95$, $p = 0.067$; $f_3/f_2 = 0.675$, $t = 3.42$, $p < 0.01$). There is no evidence of statistically significant mating interaction or frequency-dependent fertility.

Frequency trajectories, as estimated with the marker locus in the long-term

TABLE 5

Summary of progeny observed in Fertility Crosses I to IV

Cross	Reps	Estimator	Fertility experiments Total progeny XX	X_rX	X_rX_r	N	Estimator mean
I	12	f_1/f_2	937	263	—	1280	0.83
II	12	f_1/f_2	—	990	208	1198	0.90
III	12	f_3/f_2	458	742	—	1200	0.65
IV	12	f_3/f_2	—	564	636	1200	0.70

Test	Source	Anova df	*SS*	*MS*	*F*
Mating interaction:	Among crosses	1	0.03	0.03	0.12 (NS)*
XX females	Within crosses	22	5.99	0.26	
	Total	23	6.02		
X_rX_r females	Among crosses	1	0.02	0.02	0.04 (NS)*
	Within crosses	22	8.30	0.36	
	Total	23	8.32		
Frequency dependence:	Among groups	1	0.008	0.008	0.008(NS)*
XX females	Within groups	22	2.49	0.108	
	Total	23	2.50		
X_rX_r females	Among groups	1	0.05	0.05	0.248(NS)*
	Within groups	22	4.94	0.215	
	Total	23	4.99		

* NS means not significant at 5% level.
Among-cross variance indicates mating interaction; among-group variance indicates frequency dependent mating.

population experiments, are shown in Figure 2. Two populations were lost in generation seven. The remaining eight populations were still segregating for the SR polymorphism in generation 12. Significant heterogeneity within populations over generations 9 to 12 indicates that equilibrium had not been attained. The expected trajectories shown in Figure 2 have been obtained through iteration of recurrence relations (developed in the next section), which employ the fitness estimates described above. The average behavior of the experimental populations is accurately predicted by the independent fitness estimates, as shown by the fact that the 95% confidence intervals on observed frequency trajectories contain the predicted trajectories for the first nine generations. The linear regression for expected female frequencies of SR on generations is $y = -2.31x + 56.11$, where frequencies are arc-sine transformed for normality. The best linear fit to observed frequencies of SR among females is given by $y = -2.81x + 54.35$ ($SE_b = 0.33$, $t = 8.52$, $p < 0.001$). The 95% confidence limits on the slope include the line corresponding to expected gene-frequency trajectories ($b = -2.83 \pm 0.74$). Expected trajectories among males are specified by $y = -2.39x + 53.41$. The best fit to observed trajectories is given by $y = -2.81x + 52.15$ ($SE_b = 0.31$, $t = 9.06$, $p < 0.001$). The 95% confidence limits on the slope include the line corresponding to expected trajectories ($b = -2.81x \pm 0.69$). Polynomial regression of predicted frequencies on generations reveals a slight quad-

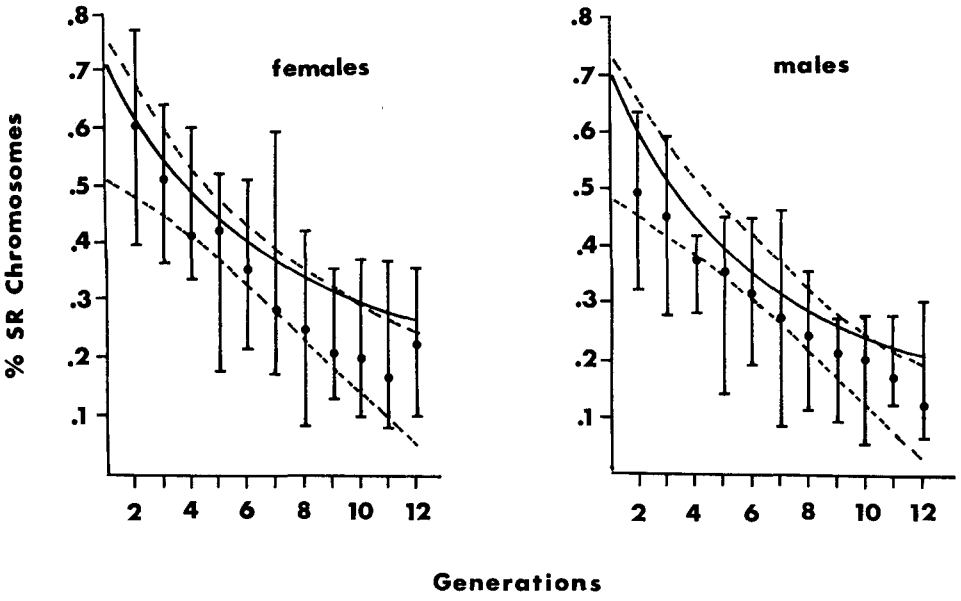

FIGURE 2.—SR frequency trajectories observed in ten long-term populations. Solid curves show expected trajectories based on independent fitness estimates; points and vertical bars show frequency means and ranges over replicates for each generation; dashed curves show the 95% prediction limits, which contain the expected trajectories for the first nine generations of the experiment.

ratic term compared to the linear term, justifying the above comparisons of linear regressions. In the final few generations, however, inclusion of the quadratic term results in a better fit; the predicted trajectories then lie completely within the 95% prediction intervals of observed trajectories. It is therefore reasonable to conclude that independently estimated fitness components are adequate predictors of SR frequency evolution in these experimental populations.

For the estimation of sexual selection in the Jasper Ridge natural population, a total of 509 isofemale lines and 551 male lines (wild-male crossed to laboratory stock female) were established in eight collections over a 26-month period. The pooled frequency of SR males was 3.3%, while the frequency of females inseminated by SR males was 3.9%. Considering the experimental bias towards underestimating SR male mating success, these data suggest that sexual selection is insufficient to account for the maintenance of the SR polymorphism in the Jasper Ridge population.

Theoretical

We present here analyses of a general model of SR evolution that incorporates sex-linkage, meiotic drive, viability, fertility and virility selection. The model is an extension of analyses presented by EDWARDS (1961), THOMSON and FELDMAN (1975), HALDANE and JAYAKAR (1964) and CANNINGS (1967). Selection parameters and genotype-frequency variables are as shown in Table 1. Suppose

SR males produce a proportion $(1+m)/2$ X_r-bearing sperm and $(1-m)/2$ Y-bearing sperm, where $0 \leq m \leq 1$. In the most general case, a fertility parameter would be assigned to each of the six possible types of matings. However, the experimental data justify a simpler model; we assume that the number of progeny produced by a mating is a multiplicative function of the fertility and virility parameters associated with the parental genotypes, *i.e.*, the male and female parents contribute independently to the number of progeny produced. A generation scheme showing all possible types of matings is shown in Table 6.

With the usual assumptions of random mating, large population size, discrete generations and constant selection coefficients, the following genotype frequency transformation equations result:

$$\begin{aligned}
TU' &= a[(1/2)(f_1v_1UX) + (1/4)(f_2v_1VX)] \\
TV' &= h[(1/4)(f_2v_1VX) + (1/2)(f_3v_1WX) + (1/2)(1+m)f_1v_2UY \\
&\quad + (1/4)(1+m)f_2v_2VY] \\
TW' &= b[(1/4)(1+m)f_2v_2VY + (1/2)(1+m)f_3v_2WY] \\
TX' &= c[(1/2)(f_1v_1UX) + (1/4)(f_2v_1VX) + (1/2)(1-m)f_1v_2UY \\
&\quad + (1/4)(1-m)f_2v_2VY] \\
TY' &= d[(1/4)(f_2v_1VX) + (1/2)(f_3v_1WX) + (1/4)(1-m)f_2v_2VY \\
&\quad + (1/2)(1-m)f_3v_2WY] \ ,
\end{aligned} \tag{1}$$

where T is the sum of the right-hand sides of (1).

Define "$\hat{r}_m$" as the equilibrium ratio of chromosome types (ST/SR) in males. Using

$$\hat{r}_m = \frac{c}{d}\ \frac{f_1\hat{U} + 1/2(f_2\hat{V})}{f_3\hat{W} + 1/2(f_2\hat{V})}$$

we obtain

$$\hat{r}_m = \frac{\hat{X}}{\hat{Y}} = \frac{c}{d}\ \frac{[f_2h(v_1c + (1+m)v_2d) - 2bdf_3v_2(1+m)]}{[f_2h(v_1c + (1+m)v_2d) - 2acf_1v_1]} \ . \tag{2}$$

TABLE 6

Mating table for the generation of genotype-frequency transformation equations

Mating	Frequency	N*	Progeny genotypes XX	X_rX	X_rX_r	XY	X_rY
$XY \times XX$	UX	f_1v_1	1/2	0	0	1/2	0
X_rX	VX	f_2v_1	1/4	1/4	0	1/4	1/4
X_rX_r	WX	f_3v_1	0	1/2	0	0	1/2
$X_rY \times XX$	UY	f_1v_2	0	$(1+m)/2$	0	$(1-m)/2$	0
X_rX	VY	f_2v_2	0	$(1+m)/4$	$(1+m)/4$	$(1-m)/4$	$(1-m)/4$
X_rX_r	WY	f_3v_2	0	0	$(1+m)/2$	0	$(1-m)/2$

Frequency and selection parameters are as defined in Table 1.

* Relative number of progeny produced by a given mating, which is a function of both the maternal and paternal genotypes.

Further substitution into the equation $U+V+W+X+Y=1$ leads to the following expressions for equilibrium genotype frequencies in terms of $\hat{r}_m$:

$$\begin{aligned}
\hat{U} &= adv_1\hat{r}_m^2/\hat{T} & \hat{V} &= [hc\hat{r}_m v_2(1+m)(v_1/(1+m)v_2 + d/c)]/\hat{T} \\
\hat{W} &= bcv_2(1+m)/\hat{T} & \hat{X} &= cd\hat{r}_m[\hat{r}_m v_1 + (1-m)v_2]/\hat{T} \\
\hat{Y} &= dc[\hat{r}_m v_1 + (1-m)v_2]/\hat{T} \ .
\end{aligned} \tag{3}$$

For valid ratios we require that the numerator and denominator of (2) have the same sign. It will be shown that, if both are positive, then polymorphism is "protected" from loss, as defined by PROUT (1968).

At the boundary corresponding to fixation of ST, $\hat{V}=\hat{W}=\hat{Y}=0$. Using the subscript "0" to indicate absence of SR, we have at equilibrium

$$\begin{aligned}
\hat{U}_0 &= a/(a+c) \\
\hat{X}_0 &= c/(a+c) \\
\hat{T}_0 &= f_1 v_1 ac/2(a+c) \ .
\end{aligned} \tag{4}$$

From the linearized equations (1), the characteristic quadratic for stability of this equilibrium is

$$\lambda^2 - \lambda[f_2 h/2f_1 a] - [f_2 d(1+m)v_2 h/2f_1 acv_1] \ . \tag{5}$$

The initial increase of SR, *i.e.*, instability of the boundary equilibrium (4), is shown by the local analysis to occur if

$$f_2 h[v_1 c + v_2 d(1+m)] > 2f_1 v_1 ac \ . \tag{6}$$

At the boundary corresponding to fixation of SR, $\hat{U}=\hat{V}=\hat{X}=0$. At equilibrium

$$\begin{aligned}
\hat{W} &= b(1+m)/[b(1+m)+d(1-m)] \\
\hat{Y} &= d(1-m)/[b(1+m)+d(1-m)] \\
\hat{T} &= f_3 v_2 b(1+m)d(1-m)/2[f(1+m)+d(1-m)] \ .
\end{aligned} \tag{7}$$

Note that if $m=1$ the system $=1$ the system degenerates. However, for $m \neq 1$, the model is biologically realistic. Local linear analysis near this point indicates that the ST chromosome increases when rare if

$$f_2 h[v_1 c + v_2 d(1+m)] > 2bdf_3 v_2(1+m) \ . \tag{8}$$

The sufficient condition for protected polymorphism when $m>0$ is therefore that the expression (2) have positive numerator and denominator. Thus, equations (6) and (8) present conditions for protected polymorphism with sex-linked meiotic drive and viability, fertility and virility selection. In order to investigate the case in which selection operates only on males, let $f_1=f_2=f_3=a=h=b=1$. The conditions for protected polymorphism then reduce to:

$$(1+m)dv_2 > cv_1 \ , \quad (1+m)dv_2 < cv_1$$

Clearly, differential fitnesses among males is not sufficient for protected polymorphism, irrespective of the degree of meiotic drive. There is no "balancing" effect of such selection comparable to heterosis at an autosomal locus. Therefore, it is reasonable to conclude that, while sexual selection and virility selection might operate on males in some natural populations, these modes of selection are not sufficient to explain the persistence of the SR polymorphism.

In the conditions (6) and (8) for protected polymorphism, we may take $h = v_1 = f_2 = 1$, without loss of generality. The conditions may then be rewritten:

$$2af_1 - 1 < v_2 d \frac{(1+m)}{c} < 1/(2bf_3 - 1) \tag{9}$$

when $2bf_3 > 1$. (If $2bf_3 < 1$, then (8) is automatically satisfied and only the first inequality of (9) is relevant.) Note that when $m = 0$, the first inequality is relatively more difficult to satisfy than when $m = 1$, while the second condition is relatively easier to satisfy. This trade off suggests that restrictiveness may not depend on m, the drive parameter. To determine the portion of the parameter space that allows protected polymorphism, we have chosen fitness parameters at random from a uniform distribution on the interval (0, 1). The proportion P of 750,000 randomly generated fitness arrays that satisfied the conditions (6) and (8) for protected polymorphism is shown below for various modes of selection, with almost complete meiotic drive ($m = 0.99$) and normal segregation ($m = 0$):

	P (m=0)	P (m=0.99)
Viability selection	0.301	0.303
Viability and virility selection	0.301	0.298
Fertility selection	0.332	0.313
Viability and fertility selection	0.339	0.339
Viability, fertility and virility	0.335	0.339

The expected value with $m = 0$ and differential fertility among females is, of course, 1/3. For all the modes of selection above, the proportion of the parameter space that allows protected polymorphism is not much different from that expected for an autosomal locus with two alleles, and is only slightly affected by the degree of meiotic drive. We do not argue that random selective forces are responsible for the maintenance of the SR polymorphism; rather, we suggest that, of all possible sets of selection coefficients, a reasonable portion allow protected polymorphism. In this sense, the group-selection hypothesis of WALLACE (1968) is unnecessary. The point may be illustrated by considering some special cases of viability selection. Let the relative viabilities of the genotypes XX, X_rX, X_rX_r, XY and X_rY equal $1-s$, 1, $1-s$, 1, and d respectively, where $s < 1$. The conditions for protected polymorphism with these heterotic fitnesses are derived from equations (6) and (8):

$$s > \frac{1-d(1+m)}{2}, \qquad s > \frac{d(1+m)-1}{2d(1+m)}. \tag{10}$$

Phase spaces illustrating these conditions for $m = 0$ and $m = 1$ are shown in Figure 3. Note that with strong heterosis ($s > 0.5$) the area of the plane in which polymorphism is allowed is identical for the $m = 0$ and $m = 1$ cases. As a second illustration, let the relative viability of the genotypes be 1, $1-s$, $(1-s)^2$, 1, and d respectively. The conditions for protected polymorphism with these multiplicative fitnesses are

$$s < \frac{d(1+m)-1}{d(1+m)+1}, \qquad s > \frac{d(1+m)-1}{2d(1+m)}. \tag{11}$$

These conditions are illustrated at the bottom of Figure 3; again, the area of the plane that allows protected polymorphism is comparable for the $m = 0$ and $m = 1$ cases. We conclude that meiotic drive has little effect on the restrictiveness of parameter choices in the conditions for protected polymorphism.

DISCUSSION

Major features of the SR polymorphism are its widespread distribution among species of Drosophila and apparent stability in natural populations. Our labora-

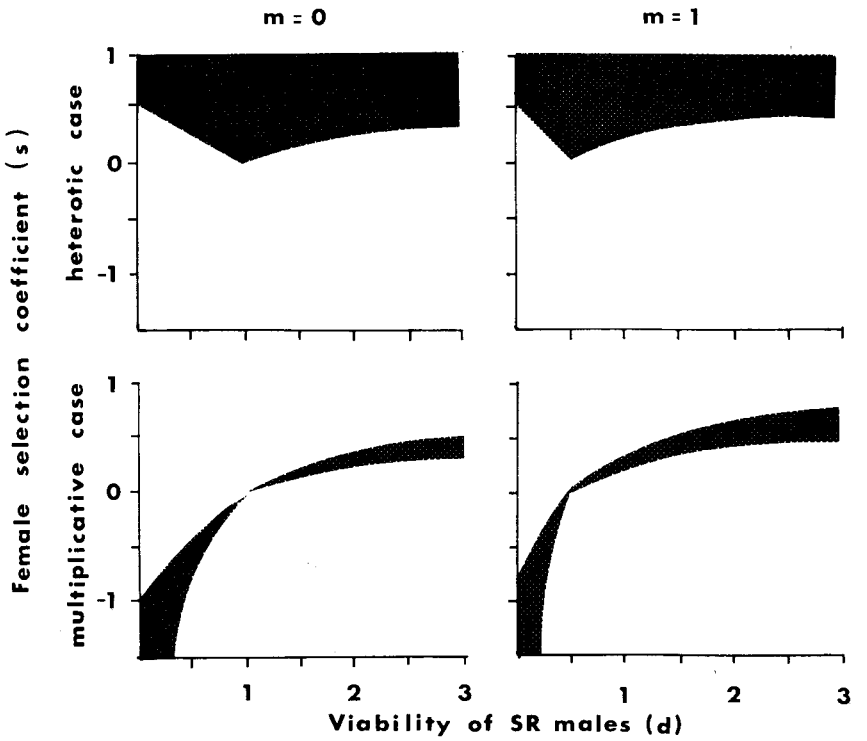

FIGURE 3.—Phase spaces illustrating conditions for protected polymorphism with heterotic or multiplicative fitnesses among female genotypes for the cases $m = 0$ (normal segregation) and $m = 1$ (complete meiotic drive). Parameter sets satisfying conditions for polymorphism are within the shaded areas.

tory fitness estimation experiments have revealed: (1) directional viability selection against SR in both males and females; (2) heterosis for fertility among females; and (3) no significant effects in virility, mating interactions or frequency-dependent mating success. A summary of the selection components analysis is shown in Table 7.

There are several limitations of the experimental method. Density-dependent selection, differential longevity and the effects of variable environments have not been considered, though the method might be extended to include such factors. Because the character under study is sex linked, several components of selection have been estimated in the absence of one or more genotypes among the progeny. We have shown that this artificiality of the method causes no problem with the viability estimates, but there could remain undetected statistical interactions in the virility and fertility parameters. The adequacy of the fitness estimates to predict gene-frequency trajectories in experimental populations has been demonstrated. When substituted into inequalities (6) and (8), the estimated fitnesses satisfy conditions for protected polymorphism. From equation (2), the predicted frequencies of SR among males and females are 11% and 14%, respectively. Observed frequencies in the Jasper Ridge population averaged 4% and 8%, respectively, over a three-year period, while the average frequencies among the experimental populations declined from 70% to 12% and 23% after 12 generations. Thus, while the fitness estimates may somewhat underestimate the intensity of selection against SR, they remain reasonably good predictors of SR frequency evolution. Of course, the major limitation of this interpretation is the unknown relationship between selective effects in the laboratory and in the field. Verification that the modes of selection found in these laboratory studies do in fact operate in nature would require either the detection of mechanisms of differential viability and fertility and ascertainment of the operation of such factors in the field, or direct fitness estimation *in situ*.

Our measurement of sexual selection in a natural population has revealed no significantly reduced mating success by SR males relative to ST males. Sexual selection and virility selection against SR males may operate in some populations,

TABLE 7

Summary of the selection-components-analysis

Fitness component	Estimator	Mean	SE	No. replicates
Viability	a/h	1.24	0.069	12
	b/h	0.55	0.046	12
	d/c	0.70	0.046	12
	a/c	1.21	0.023	126
Virility	v_2/v_1	1.03	0.074	36
Fertility	f_1/f_2	0.865	0.069	24
	f_3/f_2	0.675	0.095	24

For each estimator (except a/c) one hundred progeny were sampled per replicate. Means represent arithmetic averages over replicates, with empirical standard errors.

but, as we have shown, such phenomena cannot explain the persistence of SR polymorphism; differential fitness among males is not sufficient for protected polymorphism at a sex-linked locus, irrespective of the degree of meiotic drive. Our observation of equal virility of SR and ST males is consistent with the large body of information showing that female Drosophila must store sperm before it is utilized, and that males normally transfer much more sperm than can be stored (reviewed by FOWLER 1973). Thus, even though SR males produce fewer sperm per bundle than ST males (POLICANSKY and ELLISON 1970), the number of progeny resulting from matings with SR males is apparently not limited by the amount of sperm produced.

Our finding of strong heterosis for fertility is consistent with the results of WALLACE (1948). Viability estimates are also comparable, with the exception that directional selection is reported here, while WALLACE reported heterosis for viability; both studies found very low viability and fertility of SR homozygous females. Using the model of SR gene-frequency evolution developed here, it can be shown that WALLACE's fitness estimates satisfy conditions for protected polymorphism. The fact that two independent studies have found similar selective regimes that are sufficient for polymorphism argues strongly that the SR polymorphism is maintained by a balance between meiotic drive and counteracting viability and fertility selection. This conclusion is strengthened by our demonstration that the conditions on selection parameters for such a polymorphism are not particularly restrictive.

In addition to satisfying conditions for protected polymorphism, an adequate explanation for the persistence of the SR polymorphism should be robust with respect to perturbation of the fitness parameters. EDWARDS (1961) has pointed out that the model of meiotic drive balanced by viability selection is sensitive to small changes in the viability parameters. The model incorporating viability and fertility selection is far less sensitive to variations in the fitness parameters. The equilibrium frequency of SR among males can be studied as a function of the fitness parameters varied one at a time, with the other fitness held constant at their estimated values. Functions are derived from equation (2). In all cases, the absolute value of the slope of the functions near the estimated value is less than 1.00; thus a 1% increment in one of the fitness parameters results in less than a 1% change in the equilibrium frequency of SR.

The very low viability of SR homozygous females found here and by WALLACE (1948) is comparable to published viability estimates of whole-chromosome homozygotes; relative to chromosomal heterozygotes, whole-chromosome homozygotes show fitnesses of 0.10 to 0.33, with fair consistency over species and chromosomes (SPERLIK and KARLIK 1970; SVED 1971; TRACEY and AYALA 1974; SVED and AYALA 1970; MOURÃO, AYALA and ANDERSON 1972). Considering that the SR inversions prevent recombination over most of one chromosome arm, the low fitness of SR homozygotes in the present study may reflect the effects of homozygosity for roughly half the loci of one chromosome. Support for this interpretation comes from the work of PRAKASH (1974), who found very low levels of electrophoretic variation for four *X*-linked enzyme structural loci on

SR chromosomes. PRAKASH (1974) and PRAKASH and MERRITT (1972) chose to interpret these observations as evidence of co-adaptation of loci bound together by inversions. Considering the viability and fertility estimates presented here, an alternative explanation is that the SR inversions carry deleterious alleles, the very maintenance of which depends on linkage with meiotic drive loci.

The close association between meiotic drive loci and inversions is not unique to SR. The SD system in *D. melanogaster* and the *t*-allele system in *Mus* are also associated with recombination-modifying chromosomal arrangements (HARTL and HIRAIZUMI 1976; LYON and MEREDITH 1964). Linkage modification in segregation-distorting chromosomes is expected on theoretical grounds (THOMSON and FELDMAN 1974; HARTL 1977b). There are other similarities between the SR, SD and *t*-allele systems. SR and SD are associated with altered spermiogenesis (TOKUYASU, PEACOCK and HARDY 1972), but, unlike SR, the maintenance of the SD polymorphism seems to be explained by sterility of SD/SD males (HARTL 1977b) as a direct consequence of the mechanism of meiotic drive. SR and the lethal alleles of the *t* system, on the other hand, seem to be balanced in populations by forces other than those directly resulting from the mechanism of meiotic drive.

Is meiotic drive an important evolutionary force? Drive and other types of "abnormal" chromosome behavior have recently been reported by numerous investigators (see SVED 1976; KIDWELL, KIDWELL and SVED 1977; MATTHEWS *et al.* 1978). Our demonstration that conditions for polymorphism of sex-linked meiotic drive mutants are not restrictive suggests that such variants could be common. WHITE (1973) and MAYR (1966) argue that meiotic drive is of little evolutionary significance, while SANDLER and NOVITSKI (1957) note that meiotic drive can cause the increase of associated deleterious alleles and possibly lead to selective pressure to modify the mechanisms of meiosis. With respect to the SR polymorphism, there are several rather extreme consequences of meiotic drive, including: (1) alteration of spermiogenesis of SR males; (2) suppression of recombination over most of a chromosome arm in heterozygous females; (3) distortion of the population sex ratio towards females, with a probable positive effect on the intrinsic rate of increase; and (4) potential extinction of local populations. Few other naturally occurring polymorphisms could be said to have comparably radical consequences. Further, the existence of meiotic drive mutants forces one to ask why Mendelian segregation is stable over evolutionary time (LIBERMAN 1976; THOMSON and FELDMAN 1976; LIBERMAN and FELDMAN 1980; CROW 1979). It may not be reasonable to propose that new drive mutants are always associated with deleterious alleles that prevent their fixation. The adaptive significance of meiotic drive is also rather mysterious. Models of the evolution of drive systems do not conform to maximization of mean fitness principles, nor do they suit intuitive concepts of adaptation (THOMSON and FELDMAN 1976; CHARLESWORTH and HARTL 1978). Thus, meiotic drive seems to represent more of a genetic trap than an adaptive strategy. Finally, it must be pointed out that the frequency of meiotic drive mutants is unknown. HARTL (1977a) lists twenty cases of naturally occurring meiotic drive in commonly used experi-

mental plants and animals. Known cases are restricted to those that cause relatively large distortion of gametic ratios; lesser distortion would be more difficult to detect.

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