EXPERIMENTAL POPULATION GENETICS OF MEIOTIC DRIVE SYSTEMS.[1] III. NEUTRALIZATION OF SEX-RATIO DISTORTION IN DROSOPHILA THROUGH SEX-CHROMOSOME ANEUPLOIDY

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ABSTRACT

Laboratory populations of *Drosophila melanogaster* were challenged by pseudo-*Y* drive, which mimics true *Y*-chromosome meiotic drive through the incorporation of Segregation Distorter (*SD*) in a *T(Y;2)* complex. This causes extreme sex-ratio distrotion and can ultimately lead to population extinction. Populations normally respond by the gradual accumulation of drive suppressors, and this reduction in strength of distortion allows the sex ratio to move closer to the optimal value of 1:1. One population monitored, however, was rapidly able to neutralize the effects of sex-ratio distortion by the accumulation of sex-chromosome aneuploids (*XXY*, *XYY*). This apparently occurs because *XX*-bearing eggs, produced in relatively high numbers (~4%) by *XXY* genotypes, become the main population source of females under strong *Y*-chromosome drive. Computer simulation for a discrete generation model incorporating random mating with differences in fitness and segregation permits several predictions that can be compared to the data. First, sex-chromosome aneuploids should rapidly attain equilibrium, while stabilizing the population at ~60% males. This sex ratio should be roughly independent of the strength of the meiotic drive. Moreover, conditions favoring the accumulation of drive suppressors (*e.g.*, weak distortion, slow population extinction) are insufficient for maintaining aneuploidy, while conditions favoring aneuploidy (*e.g.*, strong distortion, low production of females) lead to population extinction before drive suppressors can accumulate. Thus, the different mechanisms for neutralizing sex-ratio distortion are complementary. In addition, *Y* drive and sex-chromosome aneuploidy are potentially co-adaptive, since under some conditions neither will survive alone. Finally, these results suggest the possibility that genetic variants promoting sex-chromosome nondisjunction may have a selective advantage in natural populations faced with sex-ratio distortion.

THE nature of the genetic mechanisms maintaining the sex ratio at or near 1:1 has been the subject of speculation from the beginning of modern evolutionary biology (DARWIN 1871) until the present time (UYENOYAMA and FELDMAN 1978 provide an excellent historical review). Setting aside the question as to whether it is the primary, secondary or some later sex ratio that is equalized, the original theoretical analyses of FISHER (1930) for selective main-

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tenance of the 1:1 ratio can be loosely paraphrased as a "grandchildren argument" (CROW and KIMURA 1970, pp. 288–289).

"Consider a population that for some reason has an excess of males .... The total contribution to the next generation is the same for males and females, and if there are fewer females, the average female produces more progeny than the average male. Now, in such a population, an individual that produces more than the average proportion of females will be producing more of that sex, which in turn contribues more to the next generation. Thus, this individual will have more grandprogeny than the average of its contemporaries. To the extent that the tendency to produce progeny wtih an altered sex ratio is hereditary, the tendency will be transmitted and the average of the population will change in the direction of equality of the sexes. Whenever the sex ratio becomes equalized, the selective advantage of the altered type will cease. The same argument holds in the opposite direction if the population has an initial excess of females."

It should be noted that this argument holds true only when the sex-ratio modification is controlled by either: (1) loci that act in the homogametic sex, or (2) autosomal loci that act in the heterogametic sex, since only in these cases is it true that the presence of the modifying element in an offspring is independent of its sex. For loci on the sex chromosomes themselves (or closely linked to the sex-determining locus in species without heteromorphic sex chromosomes), the situation is quite different (HAMILTON 1967; LYTTLE 1977, 1979). For example, *Y*-chromosome elements that cause the sex ratio to be biased towards males will always be favored in the absence of other selective forces; conversely, X-chromosome elements favoring the production of females are also selectively advantageous. Clearly, meiotic drive, where some anomaly of transmission causes one member of a pair of heterozygous alleles or heteromorphic chromosomes to be recovered in excess in the gametes (ZIMMERING, SANDLER and NICOLETTI 1970), is a potential cause for such sex-ratio deviations. These considerations form the basis for a large body of literature concerning sex-chromosome meiotic drive (THOMPSON and FELDMAN 1975; HAMILTON 1967; CANNINGS 1967; HALDANE and JAYAKAR 1964; POLIICANSKY 1974; CURTSINGER and FELDMAN 1980).

The basic conclusion reached in these several analyses is that sex-chromosome meiotic drive will increase in frequency as long as there is no overcompensating loss in fitness for the carrier of the driving chromosome. Quite simply, if a male carrying a sex-ratio-distorting *Y* chromosome produces a greater average of sons than does his normal male counterpart, for whatever reason, the distorting *Y* will increase in frequency. A similar, though less intuitive argument holds for *X*-chromosome drive (HAMILTON 1967).

Consequently, there are at least two distinct ways in which a deviant sex ratio arising from meiotic drive can be returned to 1:1; *i.e.*, either autosomal suppressors or sex chromosomes less sensitive to the distorting effects of the driving chromosome, or both, will accumulate to neutralize deviations from the optimal sex ratio. Examples of both types of suppression exist in nature. The sex-ratio (*SR*) trait, found in many species of Drosophila, is a case in point. Males carrying *SR*-type *X* chromosomes produce a great excess of female progeny under most conditions (GERSHENSON 1928; WALLACE 1968; POLICANSKY 1974; CURTSINGER and FELDMAN 1980). However, STALKER (1961) demonstrated that some populations of *D. paramelanica* have evolved insensitive *Y* chromosomes that

neutralize *SR* distortion. On the other hand, both STALKER (1961) and NOVITSKI (1947) report autosomal suppressors of *SR* activity, the latter describing a locus (*msr*) in *D. affinis*, certain alleles of which completely reverse the distortion of *SR* to give unisexual male progeny. A case of male drive in *Aedes aegypti*, male distorter (M^D), caused by a locus at or closely linked to the sex-determination locus (M = male, m = female, HICKEY and CRAIG 1966) is often found segregating with several m^d chromosomes showing different levels of sensitivity to M^D. These exhibit a range of sex ratios (= frequency of males in progeny) from ~ 0.43 to > 0.90 (WOOD 1976; SUGUNA *et al.* 1977). Similarly, several African butterfly species (where females are XY) of the genera Danaus and Acraea show Y-chromosome drive that can produce unisexual female broods (SMITH 1975; OWEN 1974). In *Danaus chrysippus*, SMITH (1975) discovered an autosomal locus, linked to loci controlling wing color and pattern, that seems partially to suppress Y drive by saving some of the X-bearing gametes that also carry the proper suppressor allele. There is some evidence that this suppressor variability may permit Danaus to use morph patterns as a cue for adjusting the sex ratio to track cyclical changes in the environment.

In an attempt to study these modes of suppression in experimental populations, my laboratory has been involved in a series of studies using the male-limited, autosomal-drive locus Segregation Distorter (*SD*) in *Drosophila melanogaster* (see HARTL and HIRAIZUMI 1976 for an excellent review). We have induced $T(Y;2)SD$ lines that effectively link *SD* and the Y chromosome Figure 1) so as to create an artificial case of Y-chromosome drive, which we call "pseudo-Y drive" or "pY drive"; and we have used pY drive to study the dynamics of populations challenged by sex-ratio distortion (LYTTLE 1977). Moreover, since *SD* is capable of complete distortion, the sex-ratio imbalance is extreme, and, according to the arguments above, this is expected to lead to a concomitantly strong selection for drive suppressors. In fact, studies surveying either natural (HARTL 1970; HARTL and HARTUNG 1975) or laboratory populations (HIRAIZUMI, SANDLER and CROW 1960; WATANABE 1967; HARTL 1977) segregating for *SD* have noted the presence of SD^+ chromosomes carrying alleles insensitive to *SD* activity (Rsp^{ins}). In addition, quantitative suppressors of *SD* activity are known to accumulate on other chromosomes (KATAOKA 1967; TRIPPA and LOVERRE 1975; LYTTLE 1979). Consequently, pY drive has the potential to elicit both types of suppresson discussed, making it extremely useful experimentally in testing the predictions of sex-chromosome-drive theory.

Pursuing this idea, LYTTLE (1979) used pY drive in experimental populations to monitor the rate at which suppressors were selected. The populations surveyed tended to accumulate unlinked polygenic suppressors at roughly a linear rate over time, with suppression measured as the net loss in M value for *SD* strength (M = the probit transformation of the proportion of SD^+ sperm surviving *SD*-mediated dysfunction in SD/SD^+ males, MIKLOS 1972). However, one population (Cage A of LYTTLE 1979) was able to neutralize pY drive through an unexpected qualitative change in the chromosomal complement—the spontaneous occurrence and subsequent selection of sex-chromosome aneuploids in the form

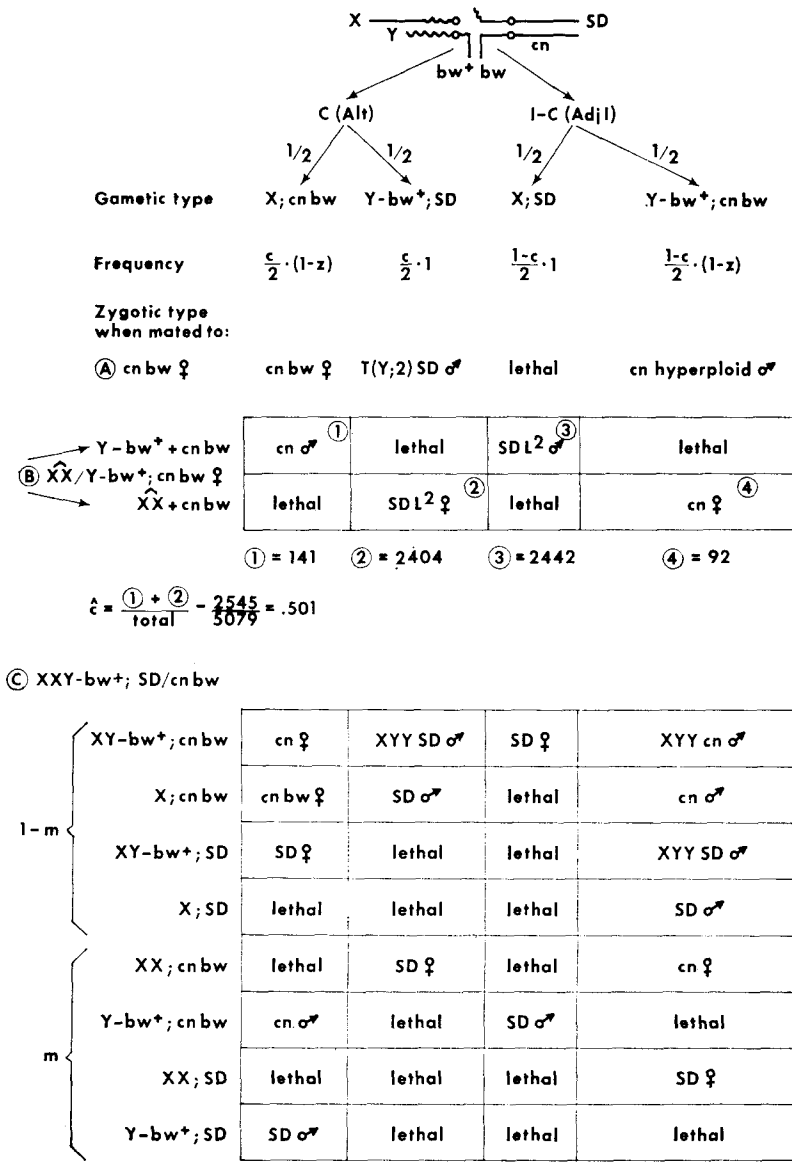

FIGURE 1.—Segregation and sex-chromosome aneuploidy in *T(Y;2),SD L²*. Note that the frequency of alternate segregation in this line (estimated from cross B) is indistinguishable from $c = 0.5$. When drive is very strong, a preponderance of the two middle columns of progeny types are produced.

of *XXY* females and *XYY* males. The lower portion of Figure 1 depicts the progeny to be obtained from a mating of a *T(Y;2)SD* male with such an *XXY* female carrying the same translocation. The hyperploid *Y*-bearing gametes produced in large numbers by such females can rescue complementarily hypoploid *X;SD* sperm, which would give lethal zygotes in matings with normal females. The

following report concerns the genetic analysis of sex-chromosome aneuploidy and other types of gross chromosomal change that can eliminate the sex-ratio distortion caused by *pY* drive, as well as the evolutionary implications that these changes pose for more general cases of true *Y*-chromosome drive.

MATERIALS AND METHODS

Stocks (for complete descriptions of *D. melanogaster* strains, see LINDSLEY and GRELL 1968): All flies were reared on standard cornmeal-molasses medium at 25 ± 1°. *cn bw*: a standard *SD+* stock, completely sensitive to distortion, which is marked with chromosome *2* eye-color mutants cinnabar (*cn*) and brown (*bw*). $\hat{X}X/Y$ *bw*$^+$; *cn bw* = *C(1)FMA4, In(1)w*^{m4} + *AB/In(1)FM7*; *y*$^-$*/Y bw*$^+$; *cn bw*. *T(Y;2), SD L*^{2}: a pseudo-*Y*-drive *SD* line, broken in division 58 of chromosome *2* just proximal to *bw*. The *Y*^{2} proportion of the translocation carries *bw*$^+$, is fully fertile by itself and survives as a hyperploid. The 2^Y portion is lethal as the deficiency. The *SD L*^{2} chromosome from which this was derived also carried the pericentric inversion of *SD-72*. This is a medium strength distorter ($k = 0.940$, where $k =$ proportion of *SD* sperm among all functional sperm produced by an *SD/SD+* male; see LYTTLE 1979 for more detail). Meiotic segregation in such males is described in Figure 1. This stock is maintained as *T(Y;2), SD L*^{2}*/cn bw*.

Competition cages (see LYTTLE 1979): Populations were initiated with 100 *T(Y;2), SD L*^{2} and 100 *cn bw* males and 500 *cn bw* females; the carrying capacity of a cage is about 1500–2000 flies. Changes in *T(Y;2)SD* frequency were measured by population census. In addition, aliquots of flies were collected from discard vials and used for k value or modifier-component analysis, according to the protocol of LYTTLE (1979). Calculations of change in *SD* strength were performed on M values, the probit transform of $z = (2k\text{-}1)/k =$ probability of *SD*-induced dysfunction of *SD+*-bearing sperm in *SD/SD+* males (MIKLOS 1972; LYTTLE 1977). The validity of this transform depends on the assumption that there is an underlying normal distribution of sperm liability to *SD* action (*cf.* the "make" value of MIKLOS 1972).

Other parameters used (see LYTTLE 1977):

$c =$ frequency segregation (*Y* + *SD* from *X* + *cn bw*) in a *T(Y;2)SD* male; defined to be 0.5 in nontranslocated lines.

$l =$ proportion of $YY \leftrightarrow X$ disjunctions in meioses of *XYY* males.

$m =$ proportion of $XX \leftrightarrow Y$ disjunctions in meioses of *XXY* females.

FY = fitness of *XYY* males relative to *XY* males.

FA = fitness of *T(Y;2)SD* males relative to *SD+* males.

$W = \dfrac{2c\text{FA}}{2\text{-}z} =$ number of sons produced per *T(Y;2)SD* male relative to an *SD+* male, including the effects of diploid fitness, meiotic drive and segregation (LYTTLE 1977).

FB, FC = relative fitness of *XXY, SD* and *XXY, cn bw* females, respectively, to *XX; cn bw* females.

For convenience, in the above definitions, we let *Y* = *Y bw*$^+$ = *Dp(2;Y) bw*$^+$; that is, the *Y*^{2} portion of *T(;2), SD L*^{2}, and *SD* = *Df(2R) bw*$^+$; *SD L*^{2}, the 2^Y portion (see RESULTS). In addition, since all flies are either *SD+/SD+* or *SD/SD+*, the superfluous *SD+* (= *cn bw* here) is generally dropped.

RESULTS

Genetic assessment of the experimental population: A graphical summary of the data reported by LYTTLE (1979, Table 3) for the reduction in *SD* strength over time in competition cages is given in Figure 2. The ordinate measures the magnitude of the decline in *SD* activity from the initial control k value of 0.940. The two open circles refer to a cage A of LYTTLE (1979), the subject of this report. Shortly after the first analysis of cage A on day 225, enough nondisjunc-

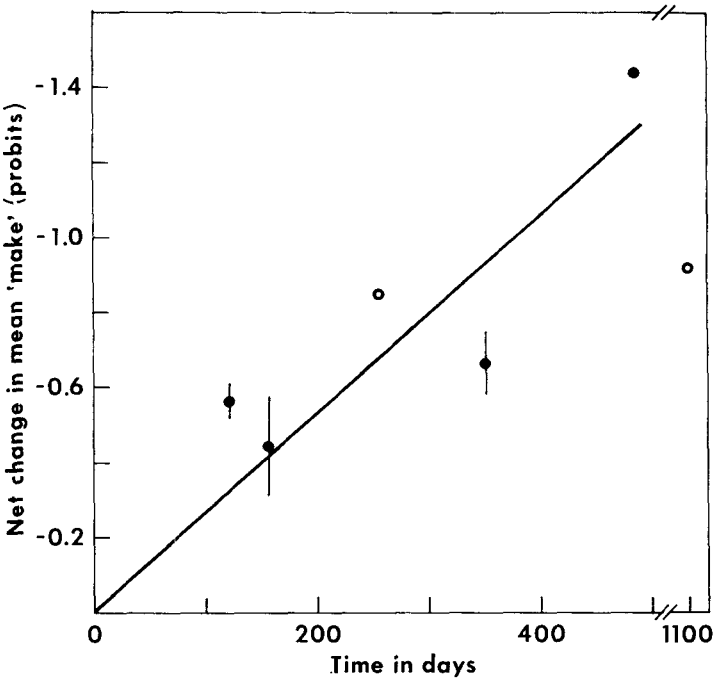

FIGURE 2.—Decrease in drive strength in *pY*-drive populations. ● = values obtained for cages other than cage A. Vertical bars represent 95% confidence intervals for the means of replicated cages. ○ = values obtained from cage A. The regression line is constrained to pass through the origin and is the best fit to all values, except for the day 1100 sample from cage A.

tional *X/X*; *T(Y;2), SD L²/cn bw* females arose to allow recombinational breakdown of the phenotypic marker complex used to identify the various genotypes. While this destroyed the value of the cage for the original experiment, the population was maintained for two more years in an attempt to see what equilibrium composition might eventually obtain. At day 1100, the cage was dismantled and the genetic structure with respect to *SD* was assayed according to the procedure in LYTTLE (1979). Surprisingly, as Figure 1 demonstrates, there was little or no further decrease in drive strength beyond that observed on day 255 ($k = 0.812$; day 1100, $k = 0.797$). Since the pattern of values obtained on day 255 and the other populations in the study seemed to predict a roughly linear regression of decreased "make" on time of about 0.03 probits per 12-day generation, this result was unexpected.

The genotypic composition of the population was also unusual, as shown by the total population census recorded in the upper half of Table 1. Males were phenotypically either + or *cn*, while females were either +, *cn cn bw* or, very rarely, *bw*. Fifty each of the + males and females were progeny tested by crossing to *cn bw* or *T(Y;2), SD L²/cn bw* flies, respectively. All of the + females proved to be *X/X*; *T(Y;2), SD L²/cn bw*, except that L^2 had been lost, presumably through recombination. Similarly, the *cn* females were determined to be *X/X/Y bw⁺;cn bw*. Among the 46 fertile + males tested, 43 proved to be

TABLE 1

Equilibrium genotype distributions

												Frequencies at equilibrium*							
												Males				Females†			
												XY;SD	*XXY;SD*	*XY*	*XYY*	*XXY;SD*	*XX*	*XXY*	*SR*
Experimental cage (based on phenotype)													±		*cn*	±	*cn bw*	*cn*	
Number observed													456		72	243	47	48	
Frequency within sex													0.874		0.126				
Progeny test partition (50 *SD* males tested)												0.817	0.057		0.126	0.719	0.130	0.142	0.608
95% confidence intervals												(0.864–0.735)	(0.010–0.139)						
Model populations: parameter value/initial frequencies																			
c	*z*	*m*	*l*	*FY*	*FA*	*FB*	*FC*	*XY;SD* ♂	*XYY;SD* ♂	*XX* ♀	GENS								
0.501	0.750	0.086	0.200	0.67	3.0	1.1	0.75	0.95	0.05	0.95	21	0.473	0.278	0.162	0.086	0.587	0.227	0.186	0.638
												0.538**	0.212	0.184	0.065				0.608
0.501	0.850	0.086	0.200	0.67	3.0	1.1	0.75	0.95	0.05	0.95	16	0.485	0.349	0.099	0.067	0.724	0.135	0.142	0.643
												0.562**	0.271	0.115	0.052				0.608
0.501	0.950	0.086	0.200	0.67	3.0	1.1	0.75	0.95	0.05	0.95	11	0.490	0.444	0.035	0.031	0.892	0.045	0.063	0.647
												0.531**	0.353	0.042	0.025				0.607

GENS = generations to equilibrium. SR = proportion males. See MATERIALS AND METHODS for definitions of the other symbols. The values for the three theoretical populations are also reproduced in Figure 3.

* *Y* = *Dp(2;Y)bw+*
SD = *Df(2R)bw+,SD*
Unlisted second chromosomes = *cn bw*.

** Measured at adult rather than zygotic stage.

† In addition, two females of genotype *XX,SD bw/cn bw* were recovered, but are not included here (see text).

standard *T(Y;2)SD/cn bw* flies, again missing L^2 from the translocation complex. However, the three remaining males carried an extra copy of *Y bw*$^+$, making them, in the shorthand of the MATERIALS AND METHODS section, *XYY;SD/cn bw*. Both the adult sex ratio and the within-sex frequencies for each of the genotypes, when known, are also tabulated in Table 1. The partitioning of the + males into their two potential genotypes is somewhat unreliable, as it depends solely on the 46 progeny tests described above, hence the 95% confidence intervals are included for these values.

These results clearly indicate that the *pY*-drive translocation had successfully eliminated the competing standard *Y* chromosome (see also LYTTLE 1979); therefore, in the following discussion we will assume that $Y = Ybw^+$. On the other hand, *pY* drive had not produced the extreme sex-ratio distortion that had been anticipated. In order to ascertain why the sex ratio and the strength of meiotic drive were not more affected, it seemed of primary importance to investigate the impact of the sex-chromosome aneuploids on the genetic structure of the population.

Theoretical analysis: A simple discrete-generation model with random mating that takes into account both the effects of segregation and differential fitness was developed in an attempt to account for the experimental data. The model allowed for four possible viable and fertile male genotypes (*XY* and *XYY*; *SD/SD*$^+$, *XY* and *XYY*; *SD*$^+$) and three female genotypes (*XX*; *SD*$^+$, *XXY*; *SD/SD*$^+$ and *XXY*; *SD*$^+$). For the data presented here, *XXYY* females that are double hyperploids for the *2R* tip are assumed to be inviable, as are *SD* homozygotes.

The expected proportions of the various gamete types produced by each of these genotypes are determined as a function of the segregation parameters (z, c, l, m) defined above. Figure 1 demonstrates the case for *XY;SD/SD*$^+$ males and *XXY;SD/SD*$^+$ females. For example, a sperm has probability c of being from an alternate segregation, 50% of receiving *X;cn bw* from that segregation, and 1-z of surviving dysfunction. This gives an absolute frequency of $c(1\text{-}z)/2$, and a relative frequency given by that quantity divided by $2/2\text{-}z$ (the total proportion of surviving sperm), or $c(1\text{-}z)/(2\text{-}z)$. Even if an *SD* male in a population cage does not produce as many successful sperm as an *SD*$^+$ male, this standardization is still appropriate, since such differences can be incorporated more readily in the fitness parameter described below. Table 2 summarizes the gamete distribution for all genotypes.

The model assumes the population is censused early enough in embryogenesis to effectively be at the zygote stage; that is, after the completely lethal aneuploids (*e.g.*, *YY* individuals and *SD* homozygotes) are removed. Consequently, a single fitness parameter incorporating both post-embryonic viability and fertility differences is used to measure the effects of selection on each genotype.

Changes in gametic frequencies in a single generation arise from both diploid selection and the effects of segregation and meiotic drive. Gametes are then combined randomly to give the zygote frequencies of the next generation. Any such model would normally also have to include the effects of recombination in *XXY;SD/SD*$^+$ females. This would generate many new genotype classes, a

TABLE 2

Gamete distribution among all genotypes

	Gametes Genotypes	$\frac{Y}{SD^+}$	$\frac{X}{SD^+}$	$\frac{XY}{SD^+}$	$\frac{YY}{SD^+}$	$\frac{Y}{SD}$	$\frac{X}{SD}$	$\frac{XY}{SD}$	$\frac{YY}{SD}$
Male genotypes	*XYY;SD*	$\frac{(1-l)(1-z)(1-c)}{(2-z)}$	$\frac{l(1-z)c}{2-z}$	$\frac{(1-l)(1-z)c}{2-z}$	$\frac{l(1-z)(1-c)}{2-z}$	$\frac{c(1-l)}{2-z}$	$\frac{l(1-c)}{2-z}$	$\frac{(1-l)(1-c)}{2-z}$	$\frac{lc}{2-z}$
	XYY;cn	$\frac{1-l}{2}$	$\frac{l}{2}$	$\frac{1-l}{2}$	$\frac{l}{2}$	0	0	0	0
	*XY;SD**	$\frac{(1-z)(1-c)}{2-z}$	$\frac{(1-z)c}{2-z}$	0	0	$\frac{}{2-z}$	$\frac{1-c}{2-z}$	0	0
	XY;cn	$\frac{1}{2}$	$\frac{1}{2}$	0	0	0	0	0	0
	Gametes Genotypes	$\frac{X}{SD^+}$	$\frac{Y}{SD^+}$	$\frac{XY}{SD^+}$	$\frac{XX}{SD^+}$	$\frac{X}{SD}$	$\frac{Y}{SD}$	$\frac{XY}{SD}$	$\frac{XX}{SD}$
Female genotypes	*XXY;SD**	$\frac{1-m}{4}$	$\frac{m}{4}$	$\frac{1-m}{4}$	$\frac{m}{4}$	$\frac{1-m}{4}$	$\frac{m}{4}$	$\frac{1-m}{4}$	$\frac{m}{4}$
	XXY;cn	$\frac{1-m}{2}$	$\frac{m}{2}$	$\frac{1-m}{2}$	$\frac{m}{2}$	0	0	0	0
	XX;cn bw	1	0	0	0	0	0	0	0

* See Figure 1c for an analysis of progeny types.

Gamete frequencies are given as functions of the sperm dysfunction and segregation parameters. In all rows, the frequencies are standardized to add to one (see text for more detail).

complication that would make the model quite unwieldy. However, the cage data of Table 1 indicate that the expected recombinant chromosome types (*SD bw* and *Df(2R)bw*$^+$;*cn*) are generally absent. In fact, only two females of presumed genotype *SD bw/cn bw* were recovered. Apparently, the only significant effect of free recombination was to allow the elimination of L^2. This is perhaps not surprising when one considers that the *Df(2R)bw*$^+$; *cn* chromosomes suffer from hypoploidy without any advantage of meiotic drive; conversely, *SD bw*-bearing males (always hyperploid for the *2R* tip) show a fitness disadvantage relative to euploid *XY*;*SD/SD*$^+$ males. Moreover, recombinant eggs are largely fertilized by *T(Y;2)SD* sperm, and, owing to the several lethals carried on the original *SD* chromosome, these generally lead to inviable zygotes. Unfortunately, the cage population was not analyzed cytologically to see whether any inversions had arisen on the *SD* chromosome to reduce recombination in *2R*. The arguments of THOMPSON and FELDMAN (1974) concerning evolution of closer linkage between drive loci and their enhancers suggest that such events are possible, which could clearly reduce the number of recombinants between the centromere and the *2R* translocation break. In any case, as a consequence of these arguments and the small number of recombinants actually observed in the final census, the effects of recombination were omitted in the simple model employed here.

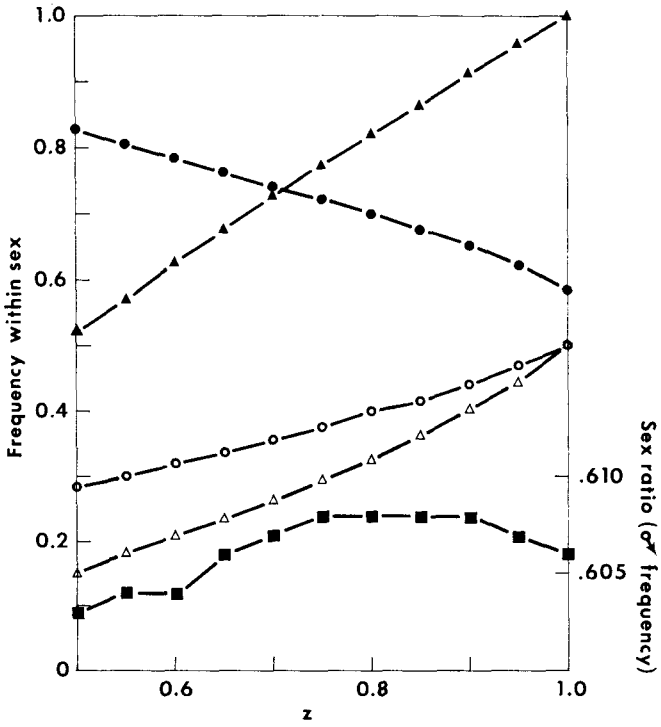

FIGURE 3.—Theoretical equilibria for sex-chromosome aneuploidy and *pY* drive. These are the results of iterations using the parametric values of Table 1. —■— = sex ratio; —●— = frequency of *XY* males; —▲ = frequency of *XXY* females; —○— = frequency of *SD* in males; —△— = frequency of *SD* in females.

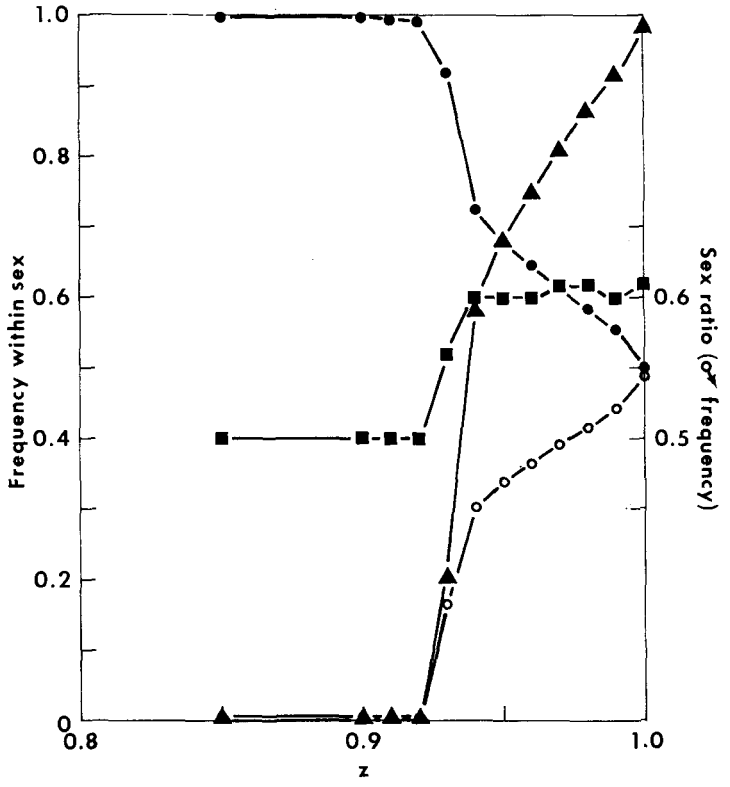

FIGURE 4.—Theoretical equilibria for sex-chromosome aneuploidy and *pY* drive. Here, no fitness differences are incorporated except viability = 0.67 for *XYY* males. Symbols are the same as for Figure 3, but note that both ordinate and abscissa values are altered.

Initial attempts to derive analytically the equilibrium sex ratio and distribution of genotypes for this model, using standard recurrence equation techniques (*cf.*, CURTSINGER and FELDMAN 1980; THOMPSON and FELDMAN 1975), proved to be prohibitively complex, owing primarily to the large number of mating types (12), the rather complicated patterns of segregation frequencies for many of the genotypes and the potential for most of these to produce the whole spectrum of possible genotypes in their progeny. Consequently, the equilibrium values were obtained directly by computer iteration (see Figures 3 and 4). The procedure was first to specify the various segregation and fitness parameters as far as possible by independent measurement. The values used are presented in Table 1. The alternate segregation parameter c for this translocation was measured by crossing *T(Y;2), SD L²/cn bw* males to *X̂X/Y bw⁺;cn bw* females (see cross B, Figure 1). The value of $c = 0.501$ is distinguishable from 0.5, as might be expected for a translocation with such distal autosomal break. The segregation parameters l and m were obtained by direct counts of the progeny of *+/B^sYy⁺/Ybw⁺;cn bw/CyO* males by *cn bw* females and *y/B^sYy⁺;cn bw* males by *+/+/Ybw⁺;CyO/SD L²* females, respectively. Computations of l fall in the range $0.15 < l < 0.25$, depending on whether one assumes all sex-chromosome

types are equally viable (smaller value) or allows for a reduction in the viability of *XYY* males (GRELL 1958; LYTTLE 1981a). The value $l = 0.2$ was consequently chosen for the simulation analysis. The same crosses also yield the viability (and by inference, the approximate total fitness) estimate for *XYY* males of $FY = 0.67$. The value of m obtained (0.022) was somewhat lower than, but compatible with, BRIDGES' (1916) value of $m = 0.086$; hence, the latter value was used. The sperm dysfunction parameter z is a variable and, as such, has no fixed value, but important reference values of z are for the *T(Y;2), SD* L^s control ($k = 0.940$, $z = 0.936$), the day 255 ($k = 0.812$, $z = 0.769$) and the day 1100 ($k = 0.797$, $z = 0.745$) cage extraction (LYTTLE 1979, Table 3).

In my laboratory, we find no change in *SD* strength for *XYY versus XY* males, and the *Df(2R)bw*$^+$*,SD* chromosome shows independent assortment from the sex chromosomes in *XYY* genotypes LYTTLE (1981a). This is contrary to the report of HIRAIZUMI (1969) and may reflect *SD* strain differences. For the purposes of this report, I will assume *SD*-sex-chromosome interactions to be of negligible importance, while recognizing the possibility of their complicating effects.

The *XY;SD* fitness can be estimated from the data of LYTTLE (1977), which suggest that $FA \sim 3.0$ for such translocations, with most of the fitness advantage attributable to virility differences. No independent estimates of female fitness (*FB,FC*) are available, so that several combinations of values were tested in the iteration procedures. Initial frequencies for the various genotypes were chosen somewhat arbitrarily, since the results of the iteration were generally independent of the starting composition of the population (for conditions under which this does not hold, see below).

Figure 3 gives the predicted equilibrium population structure for sex ratio, *SD* frequency and sex-chromosome aneuploidy, using the parameters as defined in Table 1, but allowing z to vary over a wide range. Table 1 shows the results for three specific levels of z taken from that figure. The values of *FB* and *FC* used were those giving the best fit to the observed cage results; in any case, changes in the values of these parameters have very little qualitative effect on the predictions of the model. Distributions are given both for the zygote and the adult stage, the latter simply being the proper zygotic ratios modified by the reduced viability of *XYY* males (since the other fitness differences are primarily in the fertility component—see above).

The results have several interesting features. First, for $z = 0.850$ we obtain the best fit of the theoretical predictions to the observed data. The female distribution fits extraordinarily well, while the division between + and *cn* males is also as predicted. Conversely, among the *SD* males, there seems to be a considerable excess of *XY* males, while the *XYY, SD* class is correspondingly deficient. This poor fit holds even if we allow the rather wide 95% confidence interval for the observed proportions. Furthermore, changing the magnitudes of the various parameters, either singly or jointly, does not give a significantly improved fit. When extremely high values for c ($= 0.75$) are used, the predicted frequency of *XY, SD* males rises to 0.669, but the fit of the female data deteriorates correspondingly. Basically, high frequencies of *XY;SD males* and *XXY;SD* females

should be incompatible, as Figure 3 indicates. It is not clear at this time whether this poor fit within the *SD* class is due to an inadequacy in the model structure or to an unconscious bias in the choice of the 50 *SD* males used in the progeny test, such as a tendency to choose more robust males for progeny testing, who in turn might more likely tend to be *XY* than *XYY* in genotype. However, the overall fit seems good enough to warrant the acceptance of the model as being a useful first-order predictor for the limited data set available.

Both Table 1 and Figure 3 also illustrate a striking constancy in the population sex ratio with changing z. This is especially remarkable when one considers that under normal *pY* drive, the sex ratio steadily climbs to 1.0 as z increases. The presence of sex-chromosome aneuploidy thus allows the stabilization of the sex ratio at a value (~ 0.6) very near the optimal 50% male figure. The predicted sex ratio value stays near 0.6 even when the parametric values used in the model are allowed to vary over quite a wide range. It should be noted that the embarrassingly close fit of the observed to the predicted sex ratio may not be quite as good as it appears owing to the tendency for Drosophila population cages generally to show a slight excess of males. This might force the expected ratio to a value somewhat higher than that obtained here.

Accepting the fit of the data to the model, we can turn to a general examination of Figure 3. LYTTLE (1977) showed that for *pY*-drive males to continue to increase in frequency (and thus increase the sex ratio), their relative fitness, $W = 2cFA/(2\text{-}z)$, must exceed 1. Using the parameter values of Table 1, $W > 1$ for all z, and *SD* should always be retained by the population. For the extreme case of $z = 1$, the production of only *SD*-bearing sperm by the translocation males (Figure 1) should normally lead to eventual population extinction. A reduction in z prevents this by allowing for the production of females from $X;SD^+$-bearing sperm (LYTTLE 1979). On the other hand, when z remains at 1, production of females can occur only when hypoploid $X;SD$ sperm are rescued by $XY;SD^+$-bearing eggs, such as from *XXY* females. Thus, all surviving females are *XXY*, as Figure 3 depicts. The frequency of these females declines with z, and since *XYY* males are produced primarily by *XXY* females, their frequency is reduced proportionally. Note that since the *SD* chromosome is lethal as a homozygote, it can never exceed a frequency of 0.5. Although omitted in Figure 3, when $z < 0.5$, the curves simply continue smoothly until, when $z = 0$, aneuploidy is lost from the population, *SD* frequency approaches zero in females and 13% in males, and the sex ratio drops to 57% male. Thus, for higher values of z, the presence of aneuploidy is roughly comparable to instantaneous inactivation of *SD* in its effects on the population sex ratio.

Suppose now that we consider a more general mode of *pY* drive in which none of the specific fitness differences of Table 1 except the reduction in viability of *XYY* males is retained, while the segregation parameters remain unchanged. If we plot the predicted equilibrium population statistics with respect to z, we obtain Figure 4. For this model $FA = 1$, and consequently $W < 1$ for all $z < 0.999$; that is, *pY* drive would normally be lost from the population. Figure 4 demonstrates that in fact this expectation is realized for $z < 0.92$. For values of $z > 0.92$, however, both *pY* drive and *XYY* males continue to segregate.

Clearly, the segregational mechanics of sex-chromosome aneuploids can in certain circumstances prevent *pY*-drive-mediated population extinction by reducing the sex ratio (Figure 3, high *z*), while also helping to retain sex-ratio distortion when it might otherwise be lost (Figure 4, high *z*). In other words, sex-chromosome aneuploids can buffer a population with respect to *pY* drive. That this is so can be seen from a consideration of the relative fitness of *XX* versus *XXY* females. In general, an *XXY* female produces fewer progeny than does her *XX* counterpart; however, if both drive strength and the frequency of *XY;SD* males are elevated such that a very large proportion of sperm are aneuploid *X;SD* or *Y;SD*, then normal females at some point will have a lower expected number of daughters than *XXY* females. In terms of the "grandchildren argument", *XXY* females may have fewer progeny, but a much greater number of grandprogeny than will *XX* females; consequently, they have a fitness advantage. This advantage keeps the sex-chromosome aneuploids in the population, and, by saving aneuploid *X;SD* sperm, raises the fitness of *pY*-drive males. Thus, *SD* remains segregating when it might normally be lost. Moreover, the stronger the sex-ratio distortion, the greater this selective advantage for *XXY* females, although the effect is somewhat dependent on initial conditions. Figure 4 was generated for hypothetical populations with high initial frequencies of *SD*. When *SD* frequency is low, sex-chromosome aneuploidy is not enough to save *pY* drive under the selective conditions of the figure; apparently, too few *SD*-bearing sperm are present for *XXY* females to obtain any fitness advantage. (Nevertheless, the simulations of Figure 3 are not frequency dependent.)

A spontaneous secondary translocation: A more unusual type of change in chromosome structure appeared in a second laboratory population segregating for *pY* drive. In attempting to extract a new *XXY;SD/SD*$^+$ stock by selecting presumed nondisjunctants from this population, we discovered a female carrying a secondary translocation of the *bw*$^+$ piece to the distal tip of one *X* chromosome (broken in subdivision *1B*). The reciprocal product, the *Y* chromosome capped with an *X* telomere, was not recovered. The *X* deficiency uncovers at least the region including, and distal to, the locus for yellow (*y*). This region includes several recessive lethal loci, and indeed, the *Xbw*$^+$ chromosome is lethal in males not carrying *y*$^+$*Y* or an equivalent, though *X/Xbw*$^+$ females are apparently normal. One can hardly imagine a rearrangement more tailored to suppressing the sex-ratio distortion of *pY* drive, as Figure 1 (cross C) demonstrates. The effect of the rearrangement is to limit *X/Xbw*$^+$*;SD/SD*$^+$ females to the production of only the upper four gamete types (ignoring the *Y*, which is now missing). In addition, all male offspring receiving the *Xbw*$^+$ chromosome are inviable. When such females are mated to *XY;SD* males, as in the figure, mostly *SD* progeny with ~ 1:1 sex ratio are produced (middle columns); when mated to *XY;cn bw* males, a 2♂:3♀ sex ratio is obtained (outside columns). Thus, the overall sex ratio produced in the progeny is slightly below 1:1, and helps to compensate for the elevated sex ratio in the progeny of *XX* females (cross A). The translocation breakpoint in the *X* is distal enough to allow *X/Xbw*$^+$ to survive and reproduce quite well, but is proximal enough to cause

Xbw^+ to be lethal. Best of all, the presence of the bw^+ allows for the rescue of $X;SD$ sperm to generate more daughters, just as was the case for XXY females.

DISCUSSION

The data reported here should be viewed only as providing the stimulus for the theoretical analysis of the effect of sex-chromosome aneuploidy on populations segregating for pY drive. Clearly, experiments designed unambiguously to track the changes in the various genotype frequencies through time will be required before completely satisfactory models can be put forth. Nevertheless, the simple analysis used apparently has considerable predictive power. One puzzling weakness of the model as it stands is its inability to predict the high frequency of XY genotypes among SD males. This would appear to have nothing to do with the estimation of the fitness or segregation parameters themselves, since altering these values (as discussed above) did not significantly improve the fit. More basic refinements of the model must be sought.

The sex-ratio predictions (which are, after all, the most important) are quite good. It is remarkable that the equilibrium sex ratio of Figures 3 and 4 (for $z > 0.92$) changes so little with the probability of sperm dysfunction, z. This in turn suggests that once sex-chromosome aneuploidy arises and reaches equilibrium, further significant changes in the sex ratio cannot be achieved solely by reductions in the strength of meiotic drive. The puzzling data of Figure 2 could be explained on this basis. That is, relaxation of downward selection on z after the establishment of sex-chromosome aneuploidy would be expected to lead to the constancy of drive strength observed over the time between the two population samples from Cage A.

Sex-chromosome aneuploidy is most important when drive is strong and pY males are numerous, as the figures show. These are also the conditions favoring rapid attainment of equilibrium (Table 1). Conversely, reduction of the sex ratio through slow accumulation of drive suppressors (LYTTLE 1979) is ineffective under these same conditions. Thus the optimum response to drive-mediated sex-ratio distortion apparently shifts with the strength of drive. For low z, the sex ratio is only mildly distorted, and the population has a long time in which to inactivate the meiotic drive. Sex-chromosome aneuploids presumably would not become established because of their decreased fecundity. For high z, the population must react rapidly to avoid extinction, and the small but significant proportion of spontaneous sex-chromosome aneuploids offers just such a mechanism for quick neutralization of sex-ratio distortion.

Other types of chromosome structural change, providing similar mechanisms for altering the sex ratio, also appear to have a selective advantage. The spontaneous secondary translocation described here is a case in point. The fact that these variants arise and selectively increase in populations of a few hundred flies maintained over a few dozen generations is an awesome indication of the strength of the selection involved in maintaining a balanced sex ratio.

A further point of interest is the observation that sex-ratio aneuploids buffer a population with respect to the pY drive. Once aneuploids are established, not

only can they prevent population extinction, but they can also prevent drive from being lost under fitness regimens that would normally lead to its elimination (Figure 4). Thus, meiotic drive and sex-chromosome aneuploids are in some sense co-adapted: under certain conditions, neither can survive alone. In addition, frequency dependence plays a part, since the fitness of *XXY* females depends on having both strong drive and high frequency of *pY*-drive males.

One might question whether these results, obtained from a rather contrived case of *pY*-chromosome drive, have any evolutionary applicability to more general cases of true sex-chromosome drive. A companion paper (LYTTLE 1981b), involving a theoretical analysis of the effect of sex-chromosome aneuploids on both *X*- and *Y*-chromosome drive, shows that qualitative results similar to those obtained here are predicted for such models. The frequency of the rarer sex for both *X* and *Y* drive depends critically on the production of either *Y*- or *XX*-bearing gametes, respectively, to reverse the usual sex of the offspring. As might be expected, aneuploidy is more important for the case of *Y* drive. The *XXY* females produced under *Y* drive are genetically the same as their mothers, and can themselves produce more exceptional females. The *XY* males from *X* drive, however, are similar to their fathers and also show *X* drive. Therefore, aneuploidy is not self-sustaining under the latter case, requiring the constant input of new *XXY* females.

The advantage of the extra sex chromosomes seems to be primarily in the production of relatively high numbers of *XX* gametes (~ 1–4%, LYTTLE 1981a; BRIDGES 1916) from *XXY* females. Any other genetic mechanism that allowed for increased production of sex-chromosomal, but not autosomal, nondisjunction would presumably also be selectively advantageous in populations challenged by *pY* or true *Y* drive. In particular, meiotic mutants affecting either the reductional or equational divisions might satisfy this requirement. For example, BAKER and CARPENTER (1972) report EMS-induced *X*-linked mutants defining a locus (*mei-269*) in *D. melanogaster* that seems to affect only the disjunction of *X* from *Y*. Similarly, the *X*-linked mutant equational producer (*eq*) produces large numbers of equational sex-chromosome exceptions in both sexes (BAKER and HALL 1976). If sex-chromosome drive were spontaneously arising in natural populations, such mutants might be beneficial enough to be retained in reasonable frequencies. These might be especially valuable in opposing *X*-chromosome drive, since they would provide a constant source of new aneuploid females. It is perhaps significant that SANDLER *et al.* (1968) have isolated a mutant (*mei-S332*) in a natural population that increases general nondisjunction and is partially dominant. The latter observation suggests that selective changes in frequency for such a mutant could be quite rapid, an observation of extreme importance in connection with meiotic drive. It is clearly important to test some of these variants in experimental populations challenged by *pY* drive to see if, in fact, they have a selective advantage.

Four general conclusions can be summarized: first, sex-chromosome aneuploidy offers a third mechanism, along with the accumulation of polygenic suppressors and insensitive alleles of the drive locus, for neutralizing the effects of

meiotic drive and it is most effective under conditions that do not favor the other two mechanisms. Second, aneuploidy rapidly reduces the deviant sex ratio to a nearly optimal value (~ 0.6), practically independent of the strength of drive. Third, strong *pY* drive and extra sex chromosomes are potentially co-adaptive, since under some conditions one buffers the other. Finally, it is suggested that meiotic mutants promoting sex-chromosome nondisjunction may have a selective advantage in natural populations challenged by sex-ratio distortion.

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