MODIFICATION OF RECOMBINATION FREQUENCY IN DROSOPHILA. I. SELECTION FOR INCREASED AND DECREASED CROSSING OVER

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IN species consisting of diploid outbreeding individuals, genetic recombination is of great importance. By allowing reciprocal exchange of genetic material between homologous linkage groups (chromosomes), crossing over produces many different combinations of linked genes. Thus, the phenotypic variability available for the action of natural selection will be increased by the appearance of new combinations of linked genes that affect the fitness of individuals possessing them (DOBZHANSKY 1946; SPIESS and ALLEN 1961).

The selective modification of the frequency of recombination between linked genes in diploid outbreeding organisms is thought to be evolutionarily important in at least two ways. Natural selection may alter recombination frequency: (1) To adjust the rate of release of stored (potential or unexpressed) polygenic variability for quantitative traits in response to the environmental situation (MATHER 1943, BODMER and PARSONS 1962), or (2) to tighten the linkage between genes which interact epistatically to improve the fitness of individuals carrying them (FISHER 1930) so that "supergenes" are built up (SHEPPARD 1953). Elaborate mathematical models have been constructed supporting these theories (see KIMURA 1956; KOJIMA and SCHAFFER 1964; NEI 1967 and TURNER 1967). However, actual experimental data bearing on the selective modification of crossover frequency are sparse and seemingly contradictory, and very little is known about the genetic control of recombination in eukaryotes.

Several attempts to modify recombination frequency by selection have been reported for *Drosophila melanogaster*. DETLEFSEN and ROBERTS (1921) were able to decrease, but not increase, the amount of crossing over between the sex-linked genes white (*w*) and miniature (*m*). They used a selection scheme in which flies were chosen on the basis of the *X* chromosome(s) they carried (i.e., "chromosome" selection for non-crossover chromosomes for the *w–m* region in both the high and low lines) and the amount of crossing over shown by the mother in single-pair matings (i.e., "family" selection for the appropriate responses in the high and low lines). Using slightly modified but essentially similar selection schemes, MOYER (1964) was also able to decrease, but not increase, recombination between the third chromosome genes taxi and ebony but ACTON (1961) was unable to decrease recombination between the second chromosome genes cinnabar and vestigial. ACTON did not attempt to increase recombination

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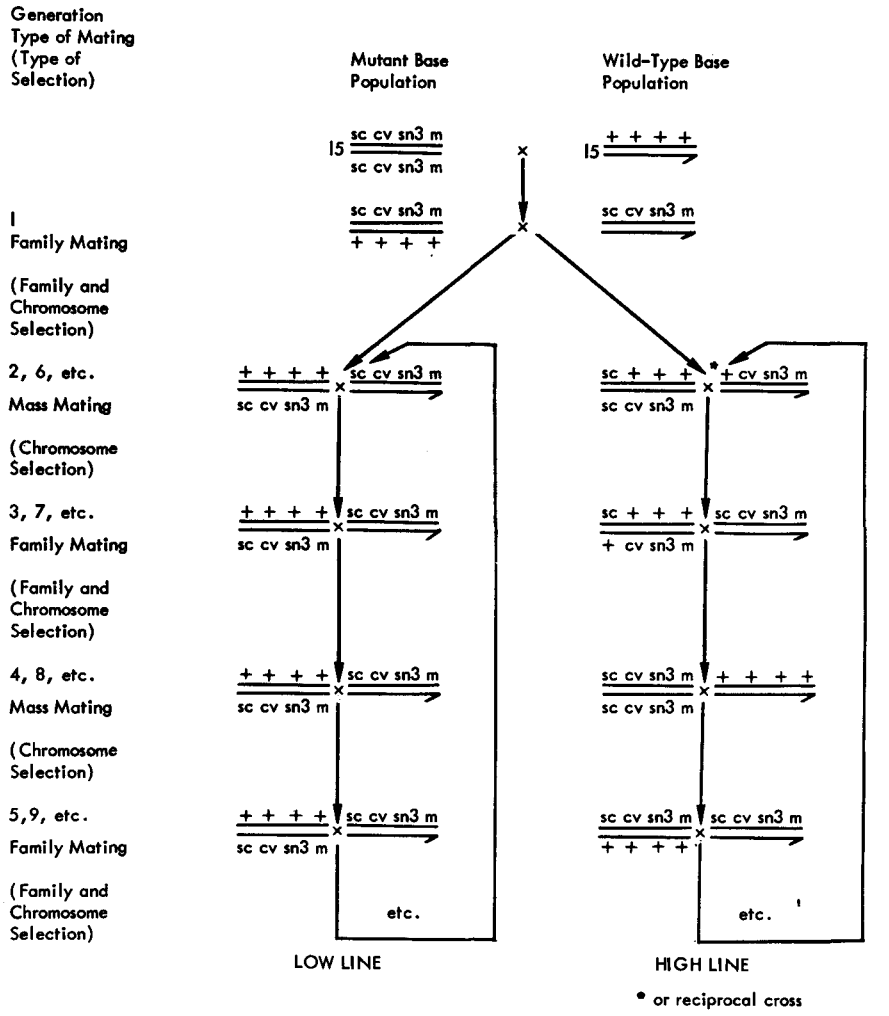

FIGURE 1.—Bidirectional selection regime practiced in the *sc–cv* region of the *X* chromosome. Flies of the listed genotypes were selected and mated either in single pairs (family) or mass matings, as indicated. See text for complete details.

in this region. PARSONS (1958) was able to increase recombination between the second chromosome genes black (*b*) and purple (*pr*) using chromosome selection alone. He selected, whenever possible, flies carrying second chromosomes which underwent a crossover event in the *b–pr* region. However, crossing over in an adjacent region, purple–vestigial (*vg*), decreased slightly so that crossing over in the overall *b–vg* region was not altered significantly by selection.

The experiment described below, using *D. melanogaster*, is an attempt to gain information concerning the following question: (1) Can selection, in fact, increase *and* decrease recombination between linked genes as theoretically predicted (see NEI and IMAIZUMI 1968)? (2) Will selective modification of crossing

over in one region of the *X* chromosome affect recombination in adjacent regions? (3) Can changes in crossover frequency occur in the absence of either chromosomal rearrangements (see LUCCHESI and SUZUKI 1968) or genes with major effects on recombination (see HINTON 1966; SANDLER *et al.* 1968)? (4) Is there a maternal effect on modifying crossing over? and (5) Does recombination frequency behave as a quantitative trait controlled by a polygenic system?

MATERIALS AND METHODS

Stocks: Three stocks of *D. melanogaster* were used during the course of the experiment: the standard laboratory stocks Oregon-R and Hikone-R and a newly synthesized stock which was homozygous for the sex-linked genes scute (*sc*, 1–0.0), crossveinless (*cv*, 1–13.7), singed (sn^3, 1–21.0), and miniature (*m*, 1–36.1). See LINDSLEY and GRELL (1968) for a full description of these mutant genes.

Mating and selection schemes: All the crosses described below were performed in a constant temperature incubator at $25 \pm 1°C$. The culture media used were standard mixtures (see CHINNICI 1970, for recipes).

Bidirectional selection for modification of recombination frequency between *sc* and *cv* was practiced as outlined in Figure 1. Two base populations were crossed, a wild-type population composed of a Hikone-R/Oregon-R mixture and the *sc–cv–*sn^3*–m* population. The F_1 progeny of this cross were then used to set up the first generation of family matings from which the high and low lines were established. After generation 1, alternating family-mating and mass-mating generations were set up.

In each family-mating generation, 20 to 40 single-pair matings were established in individual 8 dram shell vials. All female parents were 48 ± 6 hr old when initially mated. To reduce larval and pupal competition, each set of parents was periodically transferred 3 times, at 3-day intervals, into fresh vials so that each set was allowed four three-day laying periods in all. Families which produced less than 100 offspring were discarded from the population, since reliable determination of crossover percentages depends upon large numbers of scored progeny. In each line, 5 to 10 male and female progeny of the genotypes indicated in Figure 1 were selected from each of 3 to 5 families showing decreased *sc–cv* recombination in the low line and increased *sc–cv* recombination in the high line. These progeny flies were then equally distributed among 4 or 5 half-pint milk bottles and allowed to mate freely. Eight days later, the parents were removed and the progeny were allowed to complete development. Selected progeny from each mass mating were then pair mated in all possible combinations to set up the next round of family matings.

Family selection could be practiced only in odd-numbered generations, and was practiced only with regard to the amount of crossing over in the *sc–cv* region. The frequency of crossing over observed in the *cv–*sn^3 and sn^3*–m* regions did not influence the selection of families, since the crossover values in these regions were disregarded when families were selected.

Offspring from selected families were collected on the basis of the crossover history of the *X* chromosome(s) they carried. In the low line, offspring carrying *X* chromosomes derived from parental chromosomes which did not undergo crossing over between *sc–cv*, *cv–*sn^3, and sn^3*–m* were chosen. In the high line, chromosome selection favored individuals possessing *X* chromosomes which underwent a recombinational event in the *sc–cv* region while not crossing over in the *cv–*sn^3 and sn^3*–m* regions. Thus, the type of chromosome selection in the *sc–cv* region reinforced family selection in both lines, while there was no difference between the lines as far as the type of chromosome selection practiced for the *cv–*sn^3 and sn^3*–m* regions is concerned. Similar chromosome selection was also practiced upon offspring of the mass matings in the even-numbered generations.

In summary, family selection was practiced only for the *sc–cv* region, while chromosome selection was practiced in all three regions. Chromosome selection did not favor recombination between *cv–*sn^3 and sn^3*–m* in both the high and low lines, while favoring recombination between *sc–cv* in the high line and non-recombination between *sc–cv* in the low line.

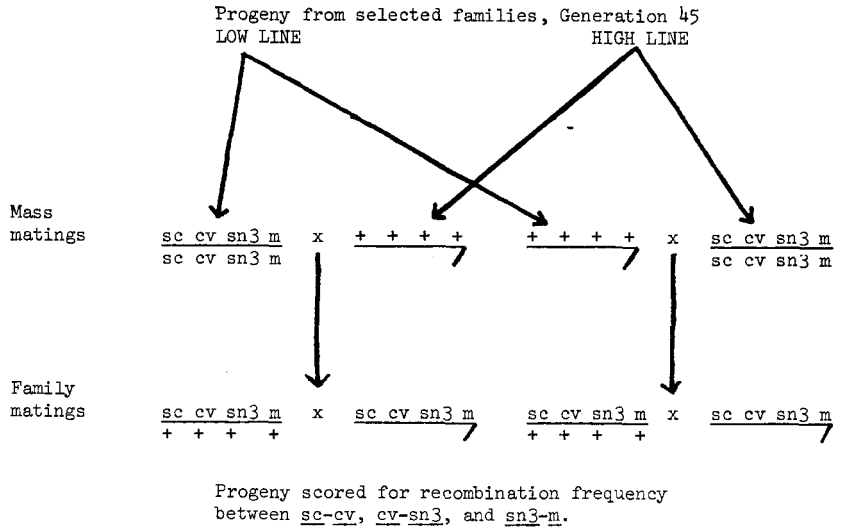

FIGURE 2.—Mating scheme for the interline (high line × low line) crosses. See text for full details.

Duration of selection: Family selection was practiced in odd-numbered generations until generation 33. After generation 33, family matings were discontinued until generation 45, and both the high and low lines were continued by mass matings only, with the chromosome selection scheme (as outlined in Figure 1) continuing unchanged. In generation 45, family matings were set up and family selection was practiced for one generation, followed again by continuous mass-mating generations.

Interline crosses: Using selected progeny from the high and low lines in generation 45, interline crosses were set up as illustrated in Figure 2. The crossover properties of the F_1 progeny from these crosses were analyzed to determine the dominance relationships between the high and low lines, as well as possible maternal effects on crossing over.

Polytene chromosome examination: Flies from both the high and low lines were checked to determine whether they carried any inversions, deletions, or translocations which could be detected by polytene chromosome examination. From the progeny of a mass-mating generation (generation 36), 20 wild-type virgin females were collected from each line. These females were mated with males from an isogenic wild-type stock derived from the standard laboratory Swedish-C strain. Female larvae from each of these crosses were collected. The salivary glands of at least six female larvae from each cross were stained with aceto-orcein and squashed. These slides were then examined microscopically for the presence of any heterologous structures.

RESULTS

Responses to selection: Recombination frequencies were determined for the *sc–cv*, *cv–sn*^{3}, *sn*^{3}*–m*, and the total *sc–m* intervals for every family in each family-mating generation. These data may be found in CHINNICI (1970). The original data from each family were first rounded off to the nearest whole percent and transformed into angular values ($P=\sin^2\phi$) as suggested by MATHER (1951). The mean recombination values and 95% confidence limits for each region were then calculated using the transformed crossover values. Finally, the angular values were transformed back into percentages, and these are given in Tables 1

TABLE 1

Results from the high recombinant line

Generation	Number of Families Examined	Progeny Number per family $\bar{x} \pm s.$	Percent Recombination sc-cv $\bar{x}$	Percent Recombination cv-sn3 $\bar{x}$	Recombination sn3-m $\bar{x}$	Recombination sc-m $\bar{x}$	Number of Families Selected	Mean Recombination Values for Selected Families sc-cv	cv-sn3	sn3-m	sc-m
1	58	226 ± 66	15.4	8.1	16.3	40.5	3	19.9	9.3	17.7	47.7
3H	22	260 ± 62	16.0	8.0	15.6	40.0	5	18.5	9.0	15.2	43.0
5H	30	182 ± 39	18.4	9.2	16.0	43.9	5	22.0	10.0	16.9	49.0
7H	27	219 ± 38	16.8	8.4	15.3	40.7	5	20.7	8.4	16.7	46.3
9H	24	130 ± 22	17.6	7.9	15.7	41.8	4	22.7	9.3	17.5	50.0
11H	27	316 ± 63	17.6	8.0	15.6	41.6	5	23.0	8.7	15.3	47.6
13H	17	219 ± 46	18.2	8.7	14.6	41.8	3	21.7	8.6	14.3	45.0
15H	20	196 ± 37	19.5	7.6	15.6	43.2	3	24.3	6.6	18.0	49.3
17H	20	217 ± 32	19.0	7.5	14.2	41.0	3	22.6	9.9	11.8	44.6
19H	19	228 ± 52	21.9	8.2	15.0	45.5	3	24.3	8.6	14.0	47.0
21H	29	194 ± 47	20.5	7.8	15.0	43.5	3	23.0	7.2	18.0	48.3
23H	19	189 ± 57	19.6	6.7	12.2	38.9	3	24.7	6.3	13.6	44.7
25H	20	197 ± 35	19.8	7.3	14.7	42.1	3	21.7	6.9	13.5	42.3
27H	17	254 ± 38	19.1	7.1	13.2	39.9	3	22.3	8.6	13.3	44.3
29H	18	238 ± 44	18.9	7.0	14.5	40.6	3	21.3	6.6	13.8	42.0
31H	18	152 ± 22	21.7	6.9	14.3	43.4	3	25.0	6.3	13.6	45.3
33H	19	225 ± 47	22.1	7.0	16.3	46.3	3	22.3	7.7	16.0	46.0
45H	19	200 ± 43	21.6	6.4	14.7	42.9	3	24.0	7.6	13.6	45.3

The number of families and the mean family size in each generation is given, along with mean recombination values for each of the three *X*-chromosome regions under study, and their sum. Recombination values from selected families is also given.

TABLE 2

Results from the low recombinant line

Generation	Number of Families Examined	Progeny Number per family $\bar{x} \pm s.$	Percent sc-cv $\bar{x}$	Percent cv-sn3 $\bar{x}$	Recombination sn3-m $\bar{x}$	Recombination sc-m $\bar{x}$	Number of Families Selected	Mean Recombination Values for Selected Families sc-cv	cv-sn3	sn3-m	sc-m
1	58	226 ± 66	15.4	8.1	16.3	40.5	5	13.0	8.1	16.7	38.0
3L	23	243 ± 45	15.6	7.7	16.3	40.0	3	12.7	6.6	15.6	35.3
5L	37	179 ± 40	15.7	7.9	16.0	40.0	4	12.3	6.4	14.7	33.3
7L	25	179 ± 43	15.1	8.0	16.0	39.6	5	11.3	7.9	18.2	37.5
9L	21	136 ± 21	13.7	8.3	15.7	38.2	4	9.4	9.2	14.2	33.7
11L	25	274 ± 60	12.1	8.2	14.6	35.4	5	8.6	7.6	14.3	30.9
13L	17	182 ± 35	11.6	8.7	14.7	35.8	3	7.9	8.0	14.9	33.3
15L	17	143 ± 24	9.7	6.9	14.8	31.5	3	7.7	6.8	14.0	28.7
17L	17	169 ± 44	10.0	6.9	14.8	32.0	3	7.3	6.6	13.3	27.3
19L	17	212 ± 65	11.6	7.5	15.4	35.1	3	7.9	5.9	17.9	31.8
21L	30	192 ± 48	9.6	7.0	15.5	32.9	3	7.0	4.6	15.2	26.9
23L	17	155 ± 35	9.6	6.9	14.2	31.1	3	7.6	6.6	11.9	25.9
25L	18	186 ± 44	7.9	5.2	13.8	27.2	3	6.6	4.2	11.3	22.4
27L	17	186 ± 51	7.8	5.2	13.6	27.0	3	6.5	3.3	12.5	21.5
29L	14	197 ± 62	9.1	5.9	14.8	30.1	3	7.6	4.0	13.5	25.2
31L	15	147 ± 36	9.2	6.8	15.8	33.9	3	6.3	7.3	16.7	30.3
33L	20	221 ± 51	8.5	6.3	15.5	30.6	3	5.9	5.5	14.6	26.2
45L	20	163 ± 39	10.1	5.7	14.2	30.1	3	7.8	2.9	12.6	23.5

See Table 1 for details.

TABLE 3

Regression of mean recombination frequency on generation number (b), along with t-test values of significance for each X-chromosome region of the high and low recombinant lines

Line and region	b	$t_{(15)}$	P	High *vs.* Low $t_{(30)}$	P
High *sc–cv*	+0.1168	5.75	0.001	10.53	0.001
Low *sc–cv*	—0.2287	9.14	0.001		
High *cv–sn*^{3}	—0.0567	4.93	0.001	1.50	0.2–0.1
Low *cv–sn*^{3}	—0.0902	4.64	0.001		
High *sn*^{3}*–m*	—0.0422	2.15	.05–.02	0.19	0.9–0.8
Low *sn*^{3}*–m*	—0.0345	2.37	.05–.02		
High *sc–m*	+0.0316	1.10	0.3–0.2	5.62	0.001
Low *sc–m*	—0.2242	6.24	0.001		

See text for full details.

and 2, along with information on family size. These results are illustrated in Figures 3, 4, and 5. Recombination values from the selected families are found in Tables 1 and 2.

The regression of mean recombination frequency (in angular values) on generation number was determined for each *X*-chromosome region for the high and low lines. These values are presented in Table 3.

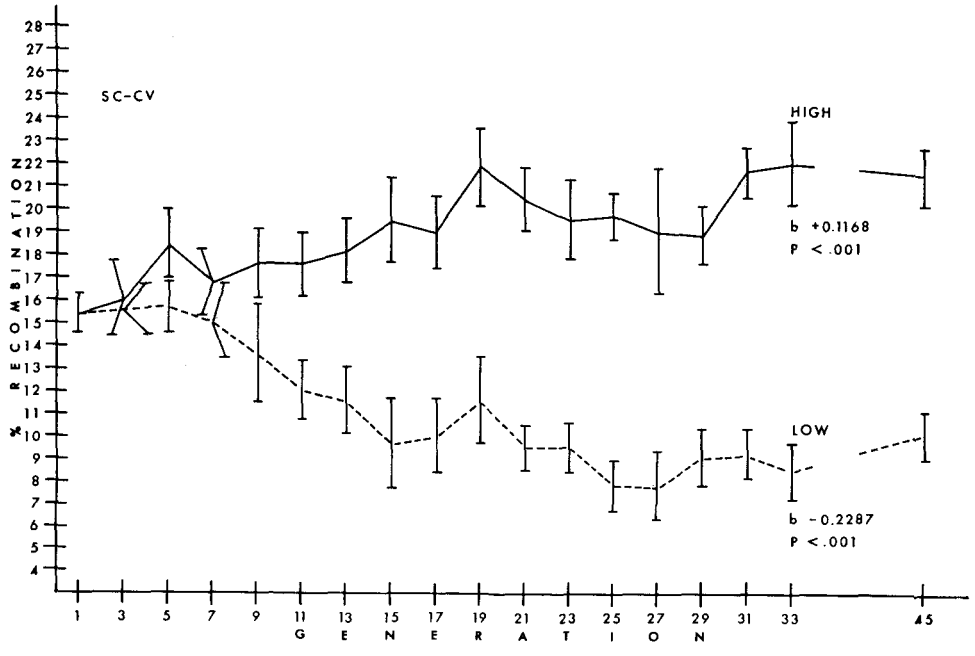

FIGURE 3.—Mean recombination values and 95% confidence limits for the *sc–cv* region of the *X* chromosome of the high and low recombinant lines.

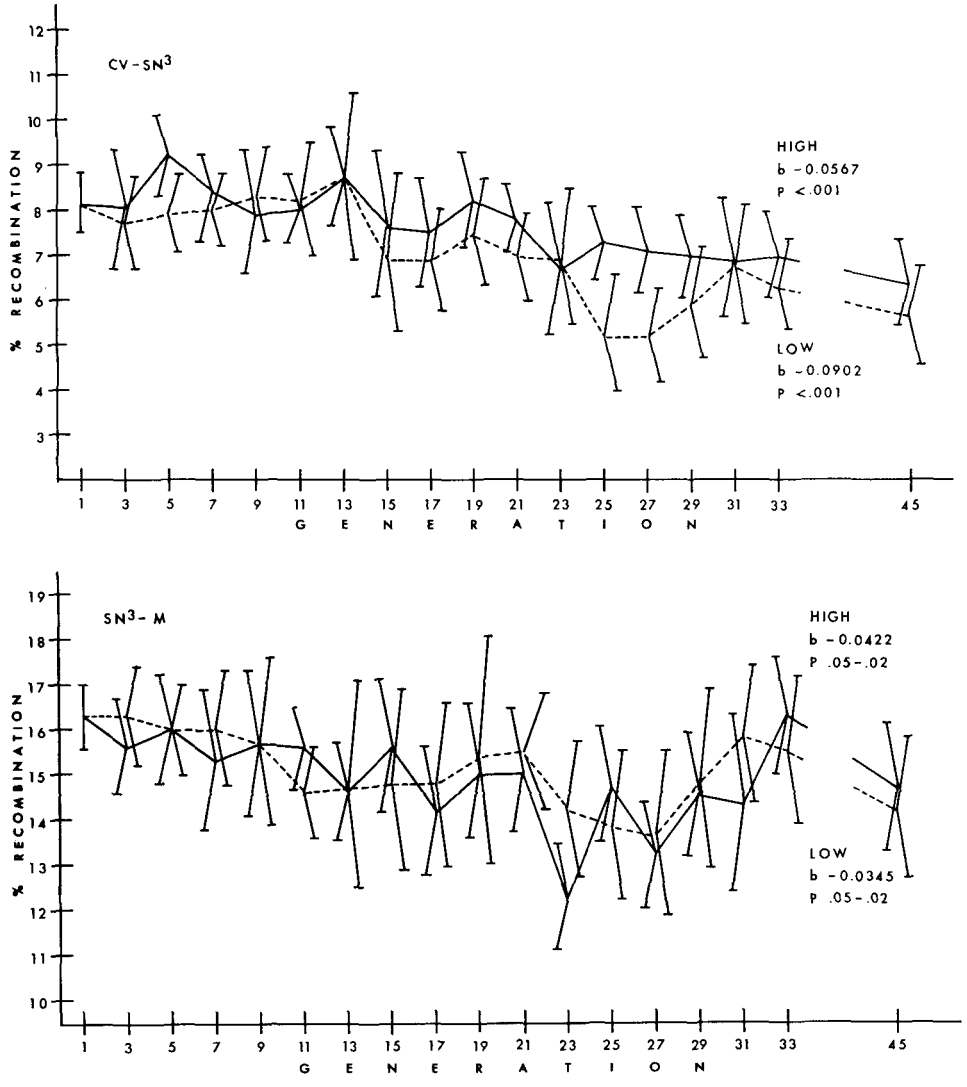

FIGURE 4.—Mean recombination values and 95% confidence limits for the *cv–sn*^{3} region of the *X* chromosome of the high and low recombinant lines.

FIGURE 5.—Mean recombination values and 95% confidence limits for the *sn*^{3}*–m* region of the *X* chromosome of the high and low recombinant lines.

The information presented in Tables 1, 2, and 3 may be summarized and correlated with selection procedures as follows: (1) *sc–cv* data. In response to family selection reinforced by selection for crossover chromosomes in the high line the mean crossover value increased from 15.4% to 22.1% in 33 generations. Regression analysis showed that this increase was very significant (see Table 3). In the low line, the mean crossover value significantly decreased from 15.4% to 8.5% in 33 generations in response to family selection reinforced by selection

of non-crossover chromosomes. (2) *cv–sn*^{s} data. In response to similar chromosome selection for non-recombination, both the high and low lines showed a significant decrease in recombination. The responses exhibited by the high and low lines did not differ significantly from each other. (3) *sn*^{s}*–m* data. In response to non-crossover chromosome selection, both the high and low lines showed a significant decrease in recombination in the *sn*^{s}*–m* region. This response to selection was very similar in the two lines. (4) *sc–m* data. In the high line, recombination in the *sc–m* interval increased, from 40.5% to 46.3% in 33 generations of selection, but this increase was not statistically significant. In the low line, the *sc–m* recombination frequency decreased significantly, from 40.5% to 30.6% in 33 generations of selection. When the responses of the high and low lines were compared, it was found that they differed significantly in their response to selection.

Interline crosses: The results of the interline crosses, outlined in Figure 2, are given in Table 4. These results show that the F_1 recombination values for all three crossover regions are roughly intermediate between the high and the low line values of the grandparents (more so when transformed values are used). The intermediate nature of the F_1 values suggests codominance of factors from the high and low lines.

Also, the F_1 recombination values from females carrying low line egg cytoplasm did not differ significantly from females carrying high line egg cytoplasm.

TABLE 4

Results of the interline crosses between flies of selected families from generation 45 of the high and low recombinant lines

Selected families from generation 45

	Progeny Number	Percent Recombination sc-cv	cv-sn3	sn3-m
High Line	254	26.0	7.9	12.2
Low Line	113	5.3	1.8	9.7

F_1 Families

Source of Female Grandparent	Family Number	Progeny No.	$\bar{x} \pm$ s.	% Recombination and 95% conf. limits sc-cv	cv-sn3	sn3-m
High Line	13	4314	331 ± 80	13.6 12.2-15.1	5.2 4.4-5.9	11.4 10.5-12.3
Low Line	18	7434	413 ± 91	12.4 11.5-13.3	5.7 5.0-6.4	12.0 11.2-12.8
Totals	31	11748	378 ± 94	12.9 12.1-13.7	5.5 5.0-6.0	11.7 11.2-12.3

Thus, there was no indication of a cytoplasmic maternal effect on recombination.

Polytene chromosome examination: The polytene chromosomes from salivary glands of female larvae from the high and low lines were examined, as described above, for the presence of heterologous structures. From the low line, six female progeny from each of 18 family matings were examined, and from the high line, six female progeny from each of 20 family matings were scored. Of the total of 108 squashes from the low line and 120 squashes from the high line, none was found to contain any inversion, translocation, deletion, or duplication detectable under the light microscope (590 ×).

DISCUSSION

The genetic system controlling recombination: The responses to selection shown by the high and low lines in this experiment indicate that recombination may be under the control of a balanced polygenic system as described by MATHER and HARRISON (1949). In the balanced polygenic model which they proposed, each chromosome contains a substantial number of linked polygenes arranged so that most if not all factors with similar effects are in repulsion to their nearest neighbors. Bidirectional response to selection may occur when a balanced linkage between polygenes is broken by recombination. If the balancing is widespread, selective advance is slow and irregular, occurring as unbalanced (coupling) chromosomes are gradually built up from their balanced (repulsion) forerunners. Spurts of rapid advance (accelerated responses) occur when like factors with relatively large effects become coupled by recombination, or when thresholds are reached through a gradual buildup of coupled like factors. Selection will no longer be effective when all polygenic loci become homozygous.

In this experiment, the high and low lines both showed gradual, slow responses to selection in the *sc–cv* region. What may be interpreted as periods of accelerated response to selection occurred during generations 11–15 and 29–31 in the high line, and during generations 7–15 and 23–25 in the low line. Apparently, in neither line had the genetic factors selected become homozygous to any great extent after 33 generations of selection, for both lines were still responding to selection at that time. Also, both lines regressed slightly towards the original crossover values during the 12 generations when only chromosome selection was practiced.

Other mechanisms besides polygenic modification of recombination are known which could cause real or apparent changes in recombination frequency. Two possibilities are structural changes in the chromosomes and selection of modifiers affecting the penetrance of a particular phenotype. Polytene chromosome examination has directly eliminated the first possibility.

Modifier systems are known which can cause change in the penetrance and/or expressivity of *sc* under directional selection (FRASER 1967). If unidirectional selection on phenotypic expression was inadvertently practiced on *sc*, the resulting change in penetrance could be confused with a change in recombination frequency between *sc* and *cv*. Two arguments may be made against this possi-

bility. In the high line, reciprocal crosses were made in generations 2, 6, etc. (see Figure 1). Thus, no consistent directional selection was practiced on modification of the *sc* phenotype. Also, in both lines, breeding data indicated that the parental flies' phenotypes always corresponded to their genotypes.

The decrease in recombination in the *sc–cv* region of the low line might have been caused either by shifting expected crossover events out of the *sc–cv* region and into adjacent regions or eliminating them completely from the chromosome. Conversely, the increase in crossing over in the *sc–cv* region of the high line might be due to either the shifting of crossover events into the *sc–cv* region from adjacent regions or the creation of new crossover events in the *sc–cv* region of the *X*. Another possibility is that recombination might have decreased in all regions in the high line. By observing the amount of recombination in regions adjacent to *sc–cv* (i.e., *cv–sn*^{s} and *sn*^{s}*–m*), it was possible to determine which of the above possibilities actually occurred.

From Table 3, it may be seen that crossing over decreased significantly in the *cv–sn*^{s} and *sn*^{s}*–m* regions in both the high and the low lines. These decreases were probably a response to selection for non-crossover chromosomes which was practiced in these regions in both lines. It is important to note, moreover, that the responses in similar regions in both lines were not significantly different. This indicates that the changes in recombination obtained in the *sc–cv* region did not affect recombination in adjacent chromosome regions, thereby eliminating the possibility of compensatory redistribution of crossover events and responses by other unselected regions of the *X*-chromosome. These results strongly indicate that the modification of crossing over in the *sc–cv* region was due to a reduction in the frequency of crossover events in the *X* chromosome in the low line, and an increase in the frequency of crossover events in the high line.

The results of chromosome substitution experiments from the high and low lines, reported elsewhere, indicate that the modification of crossing over is strongest in the *sc–cv* region of the *X* chromosome and not generally distributed over the entire genome (CHINNICI 1970, 1971). These substitution tests also show that the ability to modify crossing over is partitioned among the various chromosomes in the genome, further indicating that a polygenic system controls recombination frequency in Drosophila.

Evolutionary implications: Selection practiced at the family and chromosome levels can significantly increase or decrease the amount of recombination between sex-linked genes without structural alteration of the chromosome (at least at the light microscopic level). This selective alteration can be very specific, affecting one section of the *X* without altering recombination to a great extent in other regions of the *X*. These results argue that supergenes may be built up (or broken down) by the action of natural selection strengthening (or weakening) linkage between epistatic genes. It appears that this sort of event is not only possible but that it can occur without seriously disrupting recombination rates in adjacent chromosome regions.

The results presented indicate the presence of a polygenic system controlling crossing over. Hence, recombination must be considered a quantitative trait, and

the amount of recombination between linked genes must be, within limits, subject to modification by natural selection, just as any other continuously varying trait.

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SUMMARY

A bidirectional selection scheme was used to increase and decrease recombination between two sex-linked genes (*sc* and *cv*) in *Drosophila melanogaster*. After 33 generations of selection, recombination in the low line had decreased from 15.4% to 8.5% while crossing over in the high line had increased from 15.4% to 22.1%. Both changes are significant at the 0.001 level by regression analysis, and the gradual nature of the changes in both directions indicates a polygenic control. Polytene chromosome examination indicates that structural alterations are not responsible for these changes. Crossing over in regions adjacent to *sc–cv* (i.e., *cv–sn*^{3} and *sn*^{3}*–m*) indicates that the changes in recombination frequency observed in the *sc–cv* region are not due to a compensatory redistribution of crossover events from one region into another but rather to an increase (in the high line) and a decrease (in the low line) of crossover events in the *sc–cv* region of the *X*. High × low interline crosses indicate codominance and no maternal effect.

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