THE ORGANIZATION OF GENETIC VARIATION FOR RECOMBINATION IN *DROSOPHILA MELANOGASTER*

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ABSTRACT

The amount and form of natural genetic variation for recombination were studied in six lines for which second chromosomes were extracted from a natural population of *Drosophila melanogaster*. Multiply marked second, *X* and third chromosomes were used to score recombination. Recombination in the second chromosomes varied in both amount and distribution. These second chromosomes caused variation in the amount and distribution of crossing over in the *X* chromosome and also caused variation in the amount, but not the distribution, of crossing over in the third chromosome. The total amount of crossing over on a chromosome varied by 12–14%. One small region varied twofold; other regions varied by 16–38%. Lines with less crossing over on one chromosome generally had less crossing over on other chromosomes, the opposite of the standard interchromosomal effect. These results show that modifiers of recombination can affect more than one chromosome, and that the variation exists for fine-scale response to selection on recombination.

RECOMBINATION is one part of the genetic system of organisms. There has been much discussion about the origin and maintenance of outcrossing breeding systems (GHISELIN 1974; WILLIAMS 1975; MAYNARD SMITH 1978; BELL 1982; SHIELDS 1982; BERNSTEIN *et al.* 1985). Given that a species has an outcrossing breeding system, individual variation in recombination rates means that there can be response to selection on recombination rates. Differences in recombination rates affect the amount of genetic variation, the distribution of genotypes and the response to selection. Many factors influence whether recombination is beneficial or detrimental, several of them occurring at the same time. The nature of the genetic variation for recombination reveals on how fine a scale the genome can respond to various selection pressures on recombination rates.

Theoretical studies of the role of recombination in evolution: Various types of selection, acting alone or in combination with mutation or nonrandom mating, have been found to cause selection on recombination. This selection can be for lower or higher recombination rates. The size of the region affected

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can range from the entire genome down to particular regions. For any chromosome region, several of these forces can be acting at once. The various models are discussed in order to point out that, over the entire genome, multiple selection pressures occur on recombination.

Differences in recombination rates are most important when they cause a qualitative difference in the evolutionary dynamics. Differences in recombination rates generally cause differences in the transient behavior of gene and genotype frequencies before equilibrium is attained. Thus, recombination rate differences are important when environments fluctuate so that populations are usually not at equilibrium. When equilibria are analyzed, differences in recombination are most important when different equilibria are stable for different ranges of recombination rates, or when equilibria have different domains of attraction for different recombination rates.

Two general classes of models have been used to study how differences in recombination rates affect evolution. One class comprises selection schemes that keep loci polymorphic at equilibrium. Selection on recombination in these models has been studied almost entirely when those loci are at equilibrium. The other class comprises selection schemes that result in fixation at equilibrium. Recombination makes no difference at equilibrium, but before then can influence which alleles fix and also the rate of response to selection.

One of the first discussions of the problem was by FISHER (1930), who concluded that selection would reduce recombination; however, he gave no explicit model. KIMURA (1956) obtained this result by studying a specific model of two loci with symmetric viabilities and a recombination suppressor. NEI (1967) introduced a model with a modifier locus that affects the recombination rates between two major loci. Selection acts on recombination between the major loci by changing the frequency of alleles at the modifier locus, depending on the recombination rates they cause between the major loci. NEI found that, when additive epistasis creates nonzero linkage disequilibrium, selection decreases recombination. TEAGUE (1976) and TURNER (1967a) also reached this conclusion. Using a modifier model, FELDMAN proved that, at a stable equilibrium with both loci polymorphic and nonzero linkage disequilibrium, a modifier allele will increase in frequency if it decreases recombination between the major loci (FELDMAN, CHRISTIANSEN and BROOKS 1980).

This result applies more generally than just to the fitness schemes most studied in two-locus theory, namely additive, multiplicative and symmetric viabilities. Under any fitness scheme that can maintain both loci polymorphic with nonzero linkage disequilibrium, selection at the polymorphic equilibrium is for decreased recombination. Thus, selection has been shown to reduce recombination between interacting loci that are kept polymorphic and out of linkage equilibrium by selection.

This result raised the question posed by TURNER (1967b) "Why does the genotype not congeal?" Although general in terms of fitnesses, this result is not general in some other respects. Random mating and constant fitnesses are assumed. If the population is not at equilibrium, or the fitnesses do not result in a stable fully polymorphic equilibrium, then this result does not apply.

With directional selection the ultimate equilibrium state is fixation rather than polymorphism. Before fixation, however, different recombination rates affect the rate of response to selection. As FELSENSTEIN (1965) and TURNER (1967b) discuss, the sign of the linkage disequilibrium determines the effect of recombination, because recombination breaks down linkage disequilibrium. When favored alleles are associated, linkage disequilibrium is positive, and gene frequencies change more quickly than they would if the alleles were associated randomly. Tight linkage thus promotes the response to selection. When linkage disequilibrium is negative, favored alleles are associated with disfavored alleles. Selective differences, and therefore the response to selection, are less than if the alleles were associated randomly. High recombination rates break down this association faster than do low rates. Thus, loose linkage promotes response to selection. This dependence of the effect of recombination on the sign of the linkage disequilibrium is also shown in two-locus haploid models with recurrent mutation (ESHEL and FELDMAN 1970).

In contrast to the advantage of tight linkage for interacting polymorphic loci, FISHER (1930) and MULLER (1932) proposed that loose linkage would be advantageous for the incorporation of multiple good alleles into populations. In populations without recombination, newly arising good mutations can be incorporated into the population only if they arise in the same chromosome lineage. In populations with recombination, good mutations arising in different homologous chromosomes can eventually be recombined into the same chromosome so that they all can become fixed in the population (CROW and KIMURA 1965).

FELSENSTEIN (1974) pointed out how this FISHER-MULLER argument for the advantage of recombination is similar to the MULLER'S ratchet argument (MULLER 1964). In populations without recombination, mutation adds deleterious alleles to chromosomes, and drift eventually causes the class of chromosomes with the fewest mutations to go extinct, so that chromosomes accumulate mutations. In populations with recombination, however, chromosomes with fewer mutations than either parental chromosome can be generated. Thus, recombination allows chromosomes to be cleansed of mutations. For both the cases of incorporating many good alleles and generating mutation-free chromosomes, selection is directional. Although fitnesses may not be strictly independent across loci, the loci are not interacting strongly. The term "good" has meaning because any genotype with a good allele has higher fitness than it would without that allele. Similarly, "bad" alleles are unconditionally bad. The population is in negative linkage disequilibrium, since the chromosomes with all the good alleles or free of all the bad alleles do not exist. Higher recombination rates cause faster incorporation of good alleles and elimination of bad alleles. This advantage of higher recombination occurs over the entire genome.

A case containing elements of directional selection and polymorphic interacting loci occurs with a mutation-selection balance (FELDMAN, CHRISTIANSEN and BROOKS 1980). Selection is directional because it is always against deleterious alleles. They are maintained in the population by recurrent mutation, however, so that a stable polymorphism results. If a modifier locus is closely

linked to the major loci, then selection decreases recombination if selection on the major loci causes the initial linkage disequilibrium to be positive, and increases recombination if the initial linkage disequilibrium is negative. If the modifier locus is loosely linked to the major loci, then these effects of selection may be reversed.

KONDRASHOV (1984) studied haploid mutation-selection models with multiple loci. An unlinked modifier controls the recombination rate in the rest of the genome. When the mutation rate is low and the threshold at which multiple mutations are lethal is large, then selection can be for increased or decreased recombination in different cases. With a high mutation rate and low threshold for expressing the deleterious effects of the mutations, selection is for increased recombination.

There are other arguments about the role of recombination, based on various ecological situations such as colonizing habitats (WILLIAMS 1975), environments variable in time (MAYNARD SMITH 1978) or space (BELL 1982), and parasites (HAMILTON 1980; MAY and ANDERSON 1983). At the opposite level of analysis are arguments for the necessity of recombination in order for meiosis to occur properly.

Genetic variation for recombination: Many of the selection pressures on recombination may be occurring simultaneously. Deleterious and advantageous alleles, not interacting strongly with other loci, may cause selection for increased recombination. This selection would be genome-wide. At the same time, interacting polymorphic loci may cause selection for decreased recombination between them. This selection would occur in regions of the genome. Other selective forces on recombination, such as caused by the mating system or the longer term maintenance of variation, could also be acting.

The form of natural genetic variation will reveal how the genome can respond to these various selection pressures. The variation may be of a coarse nature, affecting the total amount of crossing over, but not the distribution of crossovers among chromosome regions. In this case, the total amount of recombination may reflect a balance among the various forces; recombination is cranked up or down over the entire genome, or large parts of it. Alternatively, the variation may be of a fine nature, affecting the distribution of crossing over, as well as the amount. In this case, local regions of chromosomes can respond to selection acting just within those regions.

Parts of the nature of genetic variation for recombination have previously been studied. Major meiotic mutants and structural heterozygosity have large effects on recombination, but we are interested in the subtler polygenic variation that SIMCHEN and STAMBERG (1969) call "fine control of genetic recombination." Recombination has been studied extensively in viruses, yeasts and other fungi (CATCHESIDE 1977), but mostly to understand the mechanism, rather than to study the variation from an evolutionary viewpoint.

The first question is simply whether genetic variation for recombination exists. Large variation in recombination rates has been found in the fungus *Schizophyllum commune* (KOLTIN, RAPER and SIMCHEN 1967; RAPER, BAXTER and ELLINGBOE 1960); recombination rates have been found to differ among

various laboratory stocks of *D. melanogaster* (LAWRENCE 1958, 1963; GREEN 1959; KIDWELL 1972a; CLEGG, HORCH and KIDWELL 1979); and selection experiments on recombination in the silkmoth *Bombyx mori* (TURNER 1979; EBINUMA and YOSHITAKE 1981) and in *D. melanogaster* (CHINNICI 1971a,b; KIDWELL 1972a,b; CHARLESWORTH and CHARLESWORTH 1985a,b) also have provided evidence of genetic variation for recombination.

However, natural selection acts not on the variation between laboratory stocks, but on the variation present in a natural population. Studying laboratory stocks does not show the magnitude or form of the variation in a natural population. Studying lines that have been selected for recombination rates, although interesting for finding modifiers, does not show the organization of the variation in nature, since genes that contribute to high or low recombination are segregated into separate lines. To understand the evolution of recombination, it is necessary to study the form of the variation that is actually present in a natural population.

This variation reflects both selective and nonselective forces, the relative importance of each unknown. Differences in recombination rates, though, do have the definite effect of causing differences in the distribution of progeny genotypes. BROADHEAD and KIDWELL (1975) found that recombination rates for two unlinked regions in *D. melanogaster* from a natural population were heterogeneous among females and were distributed roughly normally. LEVINE and LEVINE (1954, 1955) found that lines from a natural population of *D. pseudoobscura* differed in both the amount and distribution of crossovers.

In the studies that examined genetic variation for recombination in Drosophila directly, rather than through selection experiments, the genetic background came entirely, or in part, from the same lines as the chromosome being studied. Variation in chromosome maps may be due both to the chromosome being studied and to the rest of the genome. We looked at variation in the maps of several second chromosomes of *D. melanogaster* from one natural population, with the rest of the genome held constant. We also studied how these second chromosomes affected a constant pair of *X* chromosomes and a constant pair of third chromosomes. Consequently, this study reveals the form of variation due separately to linked and unlinked modifiers of recombination. This design allows us to see whether there are correlations among the chromosomes for amount of crossing over. There may be interchromosomal effects similar to those caused by inversions, with negative correlations among the chromosomes. Alternatively, there may be genome-wide effects causing positive correlations. We can also compare the effects of linked and unlinked modifiers on recombination.

Previous direct studies of the amount of variation for recombination looked at only part of a chromosome, or at an entire chromosome coarsely, with few regions. (The related selection experiment results are considered in the DISCUSSION.) They did not resolve whether the variation for recombination was due to crossing over being enhanced or reduced over the entire chromosome, or to crossovers being redistributed among the chromosome regions, or to both reasons. In this experiment we looked at almost the entire length of the

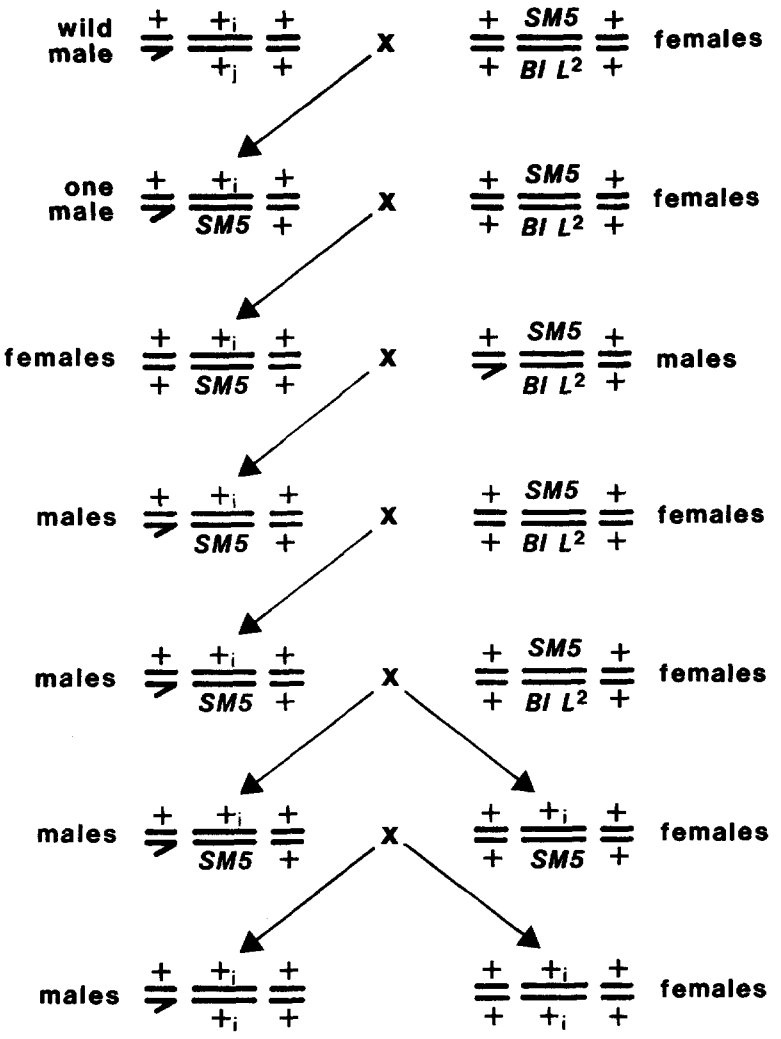

FIGURE 1.—Crosses to extract second chromosomes from wild flies. $+_i$ indicates a wild second chromosome.

chromosomes, with six regions on chromosome *2*, six regions on chromosome *3*, and three regions on the *X*. With this many regions we can see how crossing over varies for the total amount on a chromosome and for the distribution among chromosome regions.

MATERIALS AND METHODS

Wild males were supplied by P. IVES from a natural population at Amherst, Massachusetts (IVES 1970). Second chromosomes were extracted according to the scheme in Figure 1, using the balancer stock *SM5/Bl L²*, where *SM5* is *In(2LR)SM5, al² ds³³ᵏ Cy ltᵛ cn² sp²*. The chromosomes and markers are described by LINDSLEY and GRELL (1968). The extraction scheme resulted in lines homozygous for various wild second chromosomes. The five generations of crossing to the balancer stock resulted in the *X*

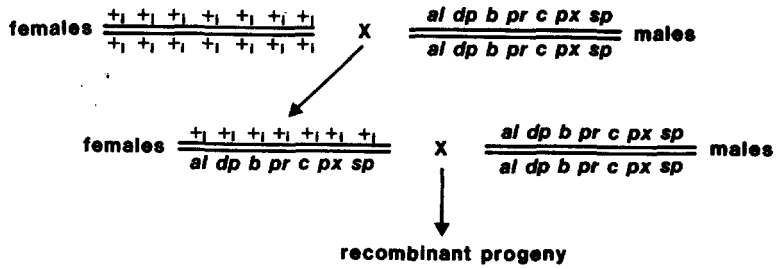

FIGURE 2.—Crosses to score recombination in the second chromosome. The second chromosomes are shown. $+_i$ indicates a wild-type allele from one of the wild second chromosomes.

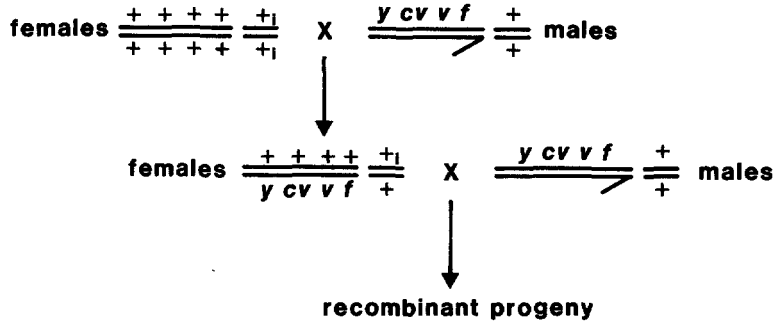

FIGURE 3.—Crosses to score recombination in the *X* chromosome. The *X* and second chromosomes are shown. $+_i$ indicates one of the wild second chromosomes.

and *Y* chromosomes and about 97% of the third and fourth chromosomes coming from the balancer stock.

The multiply marked chromosomes came from the Mid-America Drosophila Stock Center at Bowling Green State University, Ohio. The second chromosome had *aristaless, al* (2-0.01); *dumpy, dp* (2-13.0); *black, b* (2-48.5); *purple, pr* (2-54.5); *curved, c* (2-75.5); *plexus, px* (2-100.5); and *speck, sp* (2-107.0). The centromere is at 55.0. The *X* chromosome had *yellow, y* (*1*-0.0); *crossveinless, cv* (*1*-13.7); *vermillion, v* (*1*-33.0); and *forked, f* (*1*-56.7). The centromere is at 66.0. The third chromosome had *roughoid, ru* (*3*-0.0); *hairy, h* (*3*-26.5); *thread, th* (*3*-43.2); *scarlet, st* (*3*-44.0); *curled, cu* (*3*-50.0); *stripe, sr* (*3*-62.0); *ebony-sooty, e^s* (*3*-70.7); and *claret, ca* (*3*-100.7). The centromere is at 46.0. Because of the small size of the *th-st* region, its recombination rate was added to that of the *st-cu* region for all analyses.

To study recombination rates on the second chromosome, we crossed females having both a wild second chromosome and the multiply marked second chromosome with marker males and then scored their progeny for all the markers (Figure 2). To study how the second chromosome affects recombination in the *X*, we scored the progeny of females having a wild second chromosome and the second chromosome from the marked *X* stock (Figure 3). These females had the marked *X* and the *X* from the wild second chromosome line. Females that had second chromosomes from different wild second chromosome lines differed only in one of their second chromosomes; they all had the other second chromosome and the marked *X* from the marked *X* stock and one *X* originally from the balancer stock. A similar scheme was used to study how the second chromosome affects recombination in the third chromosome.

To allow for comparison with work in other laboratories, an Oregon-R line was used in the same schemes as those used for the wild second chromosome lines. However, its second chromosome was not extracted, so that its genetic background is not the same as for the other second chromosome lines.

For each of the six wild and the Oregon-R second chromosome lines, recombination

was studied in that second chromosome and in the *X* and third chromosomes. Every combination of second chromosome line and chromosome being studied for recombination was made in three replicates. For each replicate, the scheme in Figure 2 or 3 was started from the beginning. Replicates were spread out in time. The average number of flies per replicate was 730, and a total of 46,013 flies were scored.

The flies were raised at 24° on a standard cornmeal-corn syrup-agar medium in half-pint milk bottles. In the crosses to score recombination, about seven to ten females and ten males were used as parents, to control the density of the developing F_1 females. F_1 females from an 8.5-hr emergence period were used, so that recombination was scored in females of the same age. Ten of these F_1 females and ten males were used to found a bottle. They were aged together for 7 days, then were allowed to lay eggs for 3 days. Progeny were cleared each day and were scored the next, to allow pigmentation to develop. Bottles were discarded 20 days after being founded.

The lines were checked for hybrid dysgenic effects by testing for male recombination in the second chromosome. Males heterozygous for a wild and the marked second chromosomes were obtained from the same type of cross in Figure 2 that was used to produce heterozygous females. These males were backcrossed to virgin marker females, and their progeny were scored for recombination. An average of 6898 flies were scored per wild line (minimum 5885). No recombinants were found in the wild lines. Out of 7453 flies scored for the Oregon-R line, one fly was a recombinant, between *al* and *dp*. Nondysgenic males have a crossover rate of about one per 5000 (IVES 1982) anyway, whereas dysgenic males have a crossover rate of about one per 116 (SLATKO and HIRAIZUMI 1975), so there is no evidence for hybrid dysgenesis in these lines. Even though the initial cross (Figure 1) for the wild lines was in the potentially dysgenic direction, the lack of male recombination in the same type of cross used to score female recombination indicates that hybrid dysgenesis was not contributing to the variation. The lines were checked for inversions cytologically; lines with inversions were found but were not used.

The statistical analyses were done using the SAS statistical package. The recombination rates for each chromosome were analyzed by a two-way analysis of variance (ANOVA), with the recombination rates depending on line and chromosome region. The natural logarithms of the recombination rates were used because the regions varied in size, so that proportional effects on regions were more reasonable than additive effects. A significant main effect of lines means that the total amount of crossing over differs among the lines. A significant main effect of regions is always expected, and was always found ($P < 0.0001$), because the markers are not spaced evenly along the chromosome. A significant interaction between lines and regions means that the distribution of crossing over differs among the lines.

The variances were quite homogeneous for the ANOVAs of the second, *X* and third chromosomes, for both the untransformed and the logarithm transformed data (F_{max} test, SOKAL and ROHLF 1981). Although the number of flies per replicate varied, analyzing the data by the method in COCHRAN (1943) (using the error mean square) showed that this variation in replicate size was not a problem, because 96–99% of the variance was not binomial.

In a two-way ANOVA, the mean of the observed values for the cell with the *i*th line and the *j*th region is

$$LR_{ij} = m + l_i + r_j + lr_{ij},$$

where m is the overall mean, l_i is the effect of line i, r_j is the effect of region j and lr_{ij} is the interaction describing how the cell mean deviates from the additive effects of l_i and r_j (SOKAL and ROHLF 1981). The cell means can be decomposed into the separate effects by these formulas:

$$m = \text{weighted mean of all the values;}$$
$$l_i = L_i - m, \text{ where } L_i \text{ is the weighted mean value for the } i\text{th line;}$$

$r_j = R_j - m$, where R_j is the weighted mean value for the jth region;
$lr_{ij} = LR_{ij} - l_i - r_j - m$, where LR_{ij} is the mean value for the cell with line i and region j.

The weighted mean of each set of effects is zero. When the interaction in the ANOVA is significant, then these interaction values, lr_{ij}, can be graphed; they show the pattern of interactions, with all the main effects removed.

Differences in the distribution of crossing over were also analyzed by converting recombination rates into recombination proportions. Each recombination rate was divided by the total amount of recombination for that line. A two-way ANOVA was done on the arcsin of the square root of the proportions. The main effect of regions was always very significant. The main effect of lines was deliberately made zero. The line by region interaction is the only effect of interest, showing whether the lines differ in the proportions of total recombination taken up by the regions, indicating differences in the distribution of crossing over among the lines.

RESULTS

The recombination rates for each chromosome are given in Tables 1–3 and shown in Figure 4. The ANOVA results are given in Table 4. For the second and *X* chromosomes, the total amount of crossing over varied among the lines, as did the distribution of crossing over. For the third chromosome, the total amount of crossing over varied among the lines, but the distribution did not. The longest wild line was larger than the smallest by 13% for the second chromosome, 14% for the *X* chromosome and 12% for the third chromosome. The analysis of recombination proportions confirms the analysis of recombination rates; for the second and *X* chromosomes the lines differed in the distribution of crossing over.

Figure 5 shows how the distribution of crossing over on the second and *X* chromosomes differs among the lines. The line by region interactions are shown. Proportional effects are being studied, using the logarithm transformation of the data to calculate the effects and then backtransforming the additive logarithmic values to multiplicative arithmetic values. Each graphed value shows how that line-region cell differs from one, the value expected on the basis of the overall means for that line and region. Thus, the main effects of lines and regions have been removed. The patterns of values represent differences in the distribution of crossing over.

The second chromosome lines differ in distribution mostly because lines 7, 19 and 90 have one pattern, whereas lines 59, 101 and, to a lesser extent, 26 have another pattern. Large differences in the centromere region are balanced by small differences in the other regions, especially the distal regions.

The *X* chromosome lines differ in distribution mostly because lines 7 and 101 have one pattern while the others have the reverse pattern, with the largest differences in the distal regions of lines 90 and 101. The *X* chromosome is acrocentric, whereas the second and third chromosomes are metacentric. The *X* can be compared with one arm of the second chromosome. The differences are largest in the distal region and, also, in the centromere region. The interaction results from lines having disproportionately more recombination at one end of the *X* and less at the other.

Variance components can be used to compare the proportion of the variation

TABLE 1

Second chromosome recombination rates

Line	Region						Total	Replicate sample sizes		
	al-dp	*dp-b*	*b-pr*	*pr-c*	*c-px*	*px-sp*				
7	14.8 ± 0.92	29.0 ± 1.70	5.4 ± 2.27	19.0 ± 1.96	23.3 ± 1.65	6.7 ± 0.49	98 ± 3.1	532	948	978
19	13.3 ± 2.41	27.1 ± 0.40	4.9 ± 0.29	21.4 ± 1.65	23.6 ± 1.33	6.9 ± 1.42	97 ± 7.3	462	494	557
26	15.4 ± 0.49	25.4 ± 1.37	3.4 ± 0.52	17.9 ± 1.39	24.6 ± 0.47	6.5 ± 0.57	93 ± 1.4	564	591	632
59	14.5 ± 1.04	25.0 ± 1.46	2.5 ± 0.55	17.8 ± 2.33	21.1 ± 2.49	6.4 ± 1.37	87 ± 6.3	693	754	1105
90	14.4 ± 2.37	27.9 ± 2.44	5.5 ± 1.85	17.5 ± 2.87	25.2 ± 1.07	6.0 ± 1.64	105 ± 6.0	665	748	1077
101	14.0 ± 1.55	28.2 ± 0.46	3.3 ± 0.82	19.3 ± 2.07	23.5 ± 1.04	7.1 ± 1.45	95 ± 1.2	603	664	780
Ore-R	9.4 ± 2.15	28.6 ± 1.51	5.2 ± 0.52	19.5 ± 0.77	20.0 ± 0.28	6.5 ± 0.89	89 ± 5.0	469	565	665

Percent recombination, mean ± standard deviation.

TABLE 2

X chromosome recombination rates

Line	Region			Total	Replicate sample sizes		
	y-cv	*cv-v*	*v-f*				
7	14.3 ± 2.01	22.6 ± 1.14	22.0 ± 1.32	59 ± 4.2	520	565	1231
19	17.2 ± 2.23	23.9 ± 1.53	23.0 ± 1.16	64 ± 2.7	455	893	1258
26	15.2 ± 1.32	22.7 ± 1.65	19.3 ± 2.06	57 ± 4.5	487	788	939
59	15.1 ± 1.71	21.6 ± 0.94	19.8 ± 0.62	56 ± 2.6	935	1062	1064
90	18.6 ± 2.01	23.2 ± 1.99	20.9 ± 1.91	60 ± 8.6	411	715	1197
101	13.5 ± 0.71	24.2 ± 1.00	23.5 ± 0.70	61 ± 1.0	480	494	612
Ore-R	11.4 ± 2.60	21.6 ± 2.74	21.3 ± 0.83	54 ± 3.4	383	451	636

Percent recombination, mean ± standard deviation.

due to differences in the amount of crossing over with the proportion due to differences in the distribution of crossing over, aside from differences in the size of the regions. The third chromosomes differed in amount, but not in distribution of crossing over; the nonregion variation was all in the amount of crossing over. Both the second and *X* chromosomes differed for the amount and the distribution of crossing over. This variation was apportioned similarly for the two chromosomes. For the second chromosome 28% of the variation, and for the *X* chromosome 30%, was in the amount of crossing over. For the second chromosome 72% of the variation, and for the *X* chromosome 70%, was in the distribution of crossing over.

Looking at the variation among the wild lines, region by region, indicates which regions contributed most to the differences, although it does not reveal effects that are due to differences accumulated across the regions. Table 4 shows, for each region, the ratio of the largest to the smallest recombination rates. It also shows for each region the probabilities from the one-way ANOVAs testing whether the lines differed for recombination rate or proportion in that region. For a small region the variation in recombination rates among the lines was as large as twofold. In larger regions, in which the lines differ significantly, recombination rates varied by 16–38%.

For the third chromosome, in none of the regions do the lines differ significantly, even though the main effect of lines is significant. This discrepancy points out that the main effect of lines arises from effects accumulated across the regions, even though in no one region were the differences large enough to be significant.

For the second chromosome, the lines differed in the shortest and longest regions. Thus, region size does not seem to be related to whether the lines differed. These regions were a centromere and a next-to-the-centromere region. For the *X* chromosome, the lines differed in the centromere and distal regions. In centromere and distal regions the amount of recombination per unit of euchromatic length is inhibited (LINDSLEY and SANDLER 1977). These regions are sensitive to influences on recombination, such as the interchromosomal effect of inversions (SCHULTZ and REDFIELD 1951). These regions

TABLE 3

Third chromosome recombination rates

Line	Region						Total	Replicate sample sizes		
	ru-h	*h-th*	*th-cu*	*cu-sr*	*sr-e*^{s}	*e*^{s}*-ca*				
7	26.1 ± 1.79	20.4 ± 1.83	3.6 ± 1.08	12.8 ± 1.93	11.3 ± 1.03	33.2 ± 3.60	107 ± 4.3	648	1009	1485
19	25.6 ± 1.51	20.5 ± 2.65	3.5 ± 0.16	13.8 ± 1.80	9.2 ± 1.30	35.3 ± 2.42	108 ± 2.8	517	903	953
26	26.6 ± 1.82	18.0 ± 2.41	3.4 ± 1.45	11.0 ± 1.06	11.4 ± 1.09	33.1 ± 2.76	105 ± 7.4	444	640	1268
59	25.3 ± 1.66	18.4 ± 0.53	3.8 ± 1.27	11.6 ± 0.46	10.0 ± 1.06	33.0 ± 1.97	102 ± 5.0	512	720	1486
90	28.7 ± 1.66	21.0 ± 1.83	4.0 ± 0.71	12.2 ± 1.89	11.3 ± 0.37	35.6 ± 1.93	113 ± 0.4	340	476	728
101	27.2 ± 1.25	21.3 ± 3.20	5.2 ± 0.44	14.4 ± 1.03	11.0 ± 0.18	35.5 ± 1.17	114 ± 6.0	612	619	783
Ore-R	25.5 ± 1.05	21.5 ± 0.51	4.5 ± 0.30	14.3 ± 1.02	10.0 ± 0.80	35.4 ± 1.34	111 ± 1.0	423	599	726

Percent recombination, mean ± standard deviation.

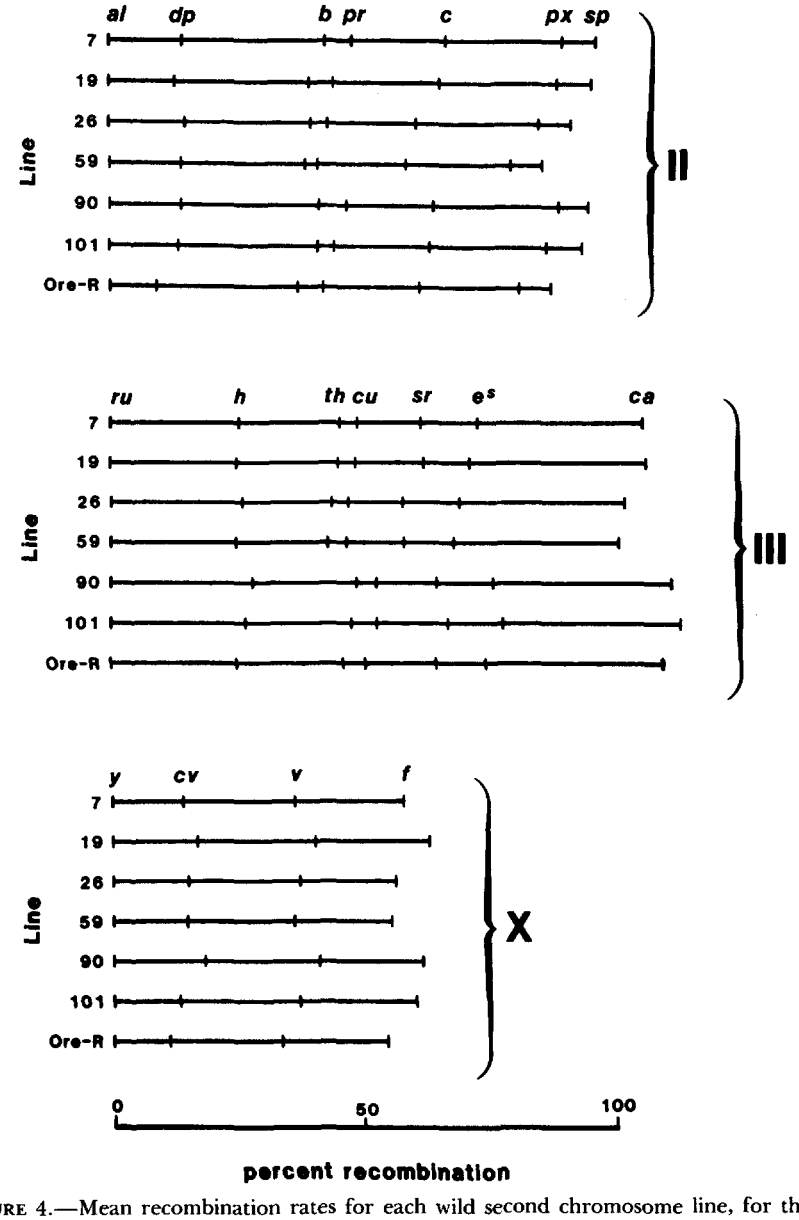

FIGURE 4.—Mean recombination rates for each wild second chromosome line, for the second, third and *X* chromosomes.

seem also to be sensitive to the modifiers affecting recombination in this experiment.

To test the consistency of the line effects across the second, third and *X* chromosomes, a two-way ANOVA was done. Recombination rates were a function of line and chromosome region, with all three chromosomes included. The significant interaction between lines and regions ($P = 0.0044$) confirmed the previous separate ANOVAs that the wild lines differed for the distribution

TABLE 4

Summary of chromosome region variation for recombination

Region	Largest/ smallest	Recombination rate ANOVA probability d.f.	Amount	d.f.	Distribution	Recombination proportion ANOVA probability d.f.	Distribution	Mean recombination rate	Mean recombination rate/ standard recombination rate
Second chromosome									
all	1.13	5	0.0088	25	0.011	25	0.0044	94.7	0.88
al-dp	1.16	5	0.69			5	0.18	14.4	1.11
dp-b	1.16	5	0.036			5	0.55	27.1	0.76
b-pr	2.20	5	0.034			5	0.058	4.2	0.69
pr-c	1.23	5	0.31			5	0.15	18.8	0.90
c-px	1.20	5	0.069			5	0.12	23.6	0.94
px-sp	1.19	5	0.89			5	0.76	6.6	1.01
X chromosome									
all	1.14	5	0.0079	10	0.0057	10	0.0001	60.1	1.06
y-cv	1.38	5	0.031			5	0.0020	15.7	1.14
cv-v	1.12	5	0.30			5	0.23	23.0	1.19
v-f	1.22	5	0.020			5	0.0026	21.4	0.90
Third chromosome									
all	1.12	5	0.0098	25	0.58	25	0.33	108.0	1.07
ru-h	1.13	5	0.23			5	0.37	26.6	1.00
h-th	1.18	5	0.37			5	0.78	19.9	1.19
th-cu	1.53	5	0.44			5	0.51	3.9	0.58
cu-sr	1.30	5	0.10			5	0.27	12.6	1.05
sr-e^s	1.23	5	0.074			5	0.093	10.7	1.23
e^s*-ca*	1.08	5	0.54			5	0.90	34.3	1.14

of crossovers. The main effect of lines is very significant ($P = 0.0001$). An *a posteriori* analysis, the REGWF test (SAS 1985), showed that lines 59 and 26 had less recombination than lines 7, 19, 90 and 101. These differences can be seen in all three chromosomes in Figure 4. The rank orders of the recombination rates, grouped by chromosome arm (Table 5), show that all five chromosome arms contributed to the main effect of lines on recombination. These analyses show that lines with less crossing over on one chromosome generally had less crossing over on the other chromosomes.

These differences in recombination were due to differences in the wild second chromosome. Since it was paired with a homologue from the marker stock, modifiers were exerting their effects in heterozygous condition. In the crosses to score recombination, the constant second chromosome was different when recombination was studied in the second, *X* or third chromosomes. The positive association for recombination among the three chromosomes thus occurred even though the homologue of the wild second chromosomes was not the same for all three chromosomes.

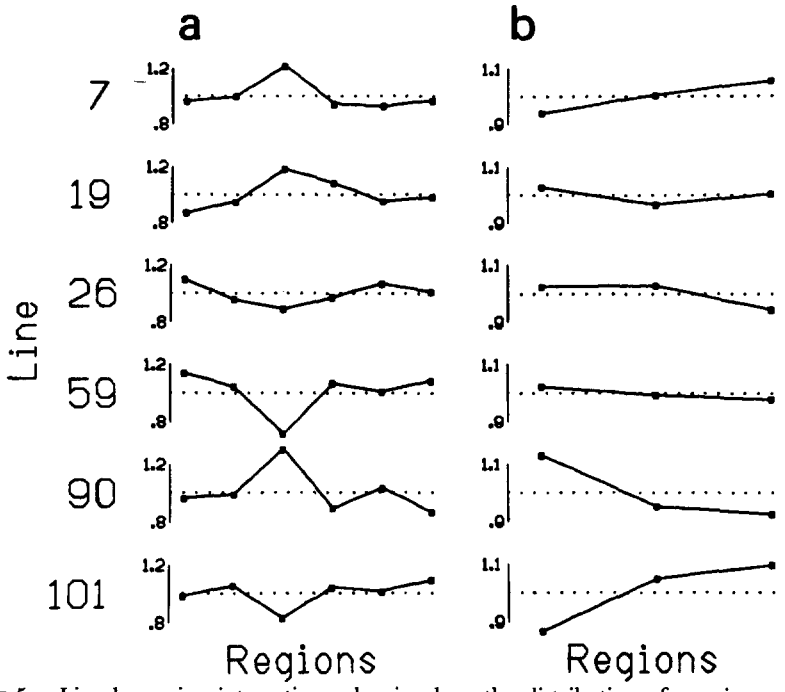

FIGURE 5.—Line by region interactions, showing how the distribution of crossing over varies among the lines. a, second chromosome. b, *X* chromosome.

TABLE 5

Rank orders for chromosome arm recombination rates

	Line					
Chromosome arm	59	26	7	19	90	101
2 left	1	2	6	3	5	4
2 right	1	3	4	6	2	5
X	1	2	3	6	5	4
3 left	1	2	4	3	5	6
3 right	1	2	3	4	5	6

Our data can be compared with the standard map distances. Table 4 shows the mean recombination rates for the wild lines, as well as their ratios to the map distances in LINDSLEY and GRELL (1968). Observed recombination rates are underestimates of the map distances for large regions because of undetected double crossovers. Our data provide more evidence that the standard map is too long for the second chromosome from *dumpy* to the centromere (MILKMAN and ZEITLER 1977). We found that centromere regions were smaller than, and distal regions were equal to or larger than, the standard distances.

Variation in epistatic viability interactions may cause some variation in the estimated recombination rates. In these experiments, however, that contribu-

tion was minor. The viabilities can be represented as follows:

Gamete	*AB*	*Ab*	*aB*	*ab*
Frequencies after meiosis	$(1 - r)/2$	$r/2$	$r/2$	$(1 - r)/2$
Fitness	1	$1 - s$	$1 - t$	$1 - s - t + e$,

where e, the epistasis parameter, measures the deviation from additive fitnesses, and r is the actual recombination rate. Both s and t are less than one. For scoring recombination, the gametes are all in genotypes with *ab*.

The observed recombination rate is

$$r' = \frac{(1 - s + 1 - t)r/2}{(1 - s + 1 - t)r/2 + (1 + 1 - s - t + e)(1 - r)/2} = \frac{r}{1 + (1 - r)e/(2 - s - t)}.$$

If the fitnesses are additive, then $e = 0$, and differences in fitness cause no variation in observed recombination rates. Actual values of e range from 0 to $s + t$. Values of e are generally positive in this sort of experiment because the multiply marked chromosomes have higher fitnesses than expected on the basis of the fitnesses of the individual markers. The maximum value of e is $s + t$ because, even with this enhanced fitness, the multiply marked chromosomes are not as fit as wild-type chromosomes. Thus, observed recombination rates are generally underestimates of the actual values. However, observed values are not compared with actual values, but are compared across lines. Differences in deviations from additivity contribute to differences in observed recombination rates.

Two lines of evidence suggest that this potentially confounding cause of variation in recombination rates is not a problem. First, the pattern of viability differences, with markers in the middle of the chromosomes not doing as well as ones on the ends, was the same across the wild lines (arcsin of the square root transformation, $P = 0.89$).

Second, viability effects of the markers on the results were kept to a minimum by redoing any replicate that had poor viabilities. Table 6 shows the proportion of alleles that were mutant for each marker locus, where 0.5 indicates no difference between the mutant and wild-type viabilities. The average viability over all the markers was 0.475 ± 0.037. Good viabilities such as these set an upper limit on how much differences in epistasis can affect observed recombination rates. The formula for the observed recombination rate, r', shows that differences in recombination enter directly through r in the numerator, plus an indirect effect in the denominator. Differences in the epistasis enter only indirectly in the denominator.

Setting s and t according to the observed mean viabilities, $1 - s = 1 - t = 2(0.475) = 0.95$; $s = t = 0.05$; $2 - s - t = 1.9$; $e_{max} = s + t = 0.1$. The formula for the observed recombination rate becomes

$$r' = \frac{r}{1 + (1 - r)e/1.9},$$

TABLE 6

Viabilities at the marker loci

Second chromosome		*X* chromosome		Third chromosome	
Locus	Mutant proportion	Locus	Mutant proportion	Locus	Mutant proportion
al	0.482	*y*	0.482	*ru*	0.473
dp	0.470	*cv*	0.478	*h*	0.457
b	0.454	*v*	0.493	*th*	0.460
pr	0.456	*f*	0.500	*st*	0.461
c	0.452			*cu*	0.459
px	0.480			*sr*	0.467
sp	0.484			*e*^{s}	0.480
				ca	0.502

where $0 < e < 0.1$. Since the maximum value of the $(1 - r)e/1.9$ term is small, a good approximation is $r' = r[1 - (1 - r)e/1.9]$.

A difference in the recombination rate affects the observed recombination rate far more than the same proportional difference in the epistasis. For example, consider a 5% change in the recombination rate r:

$$r^* = 1.05\ r\ [1 - (1 - 1.05\ r)e/1.9] = 1.05\ r\ [1 - (1 - r)e/1.9 + 0.05\ re/1.9].$$

Even with setting the last term in the brackets as large as possible, with $e_{max} = 0.1$, and $r = 36\%$ (the largest recombination rate observed in this experiment),

$$r^* = 1.05\ r' + 0.001\ r.$$

Thus, a 5% change in the actual recombination rate causes extremely close to a 5% change in the observed recombination rate.

Consider a 5% change in the epistasis e:

$$r^* = r\ [1 - (1 - r)e(1.05)/1.9] = r\ [(1 - (1 - r)e/1.9) - (1 - r)e(0.05)/1.9].$$

Even with setting the last term in the brackets as large as possible, with

$$e_{max} = 0.1, \quad \text{and} \quad 1 - r = 1,$$

$$r^* = r' - 0.0026\ r.$$

A 5% change in the epistasis causes almost no change in the observed recombination rate.

Thus, variation in recombination rates among the lines can be detected directly, whereas variation in epistatic interactions among the lines affects recombination to a much lesser extent.

The mean coefficients of coincidence for crossovers in two regions had the expected pattern in the wild lines: high interference for adjacent regions on the same chromosome arm, less interference for regions far apart on the same arm and approximately no interference for regions on opposite arms. For each of the second, *X* and third chromosomes, the wild lines do not differ signifi-

cantly for coincidence. This is so when all possible pairs of regions are considered (not including *th-st* of chromosome *3*, which is much too small for reliable results) and also when only pairs of adjacent regions are considered.

DISCUSSION

Recombination in homologous second chromosomes varied in amount and distribution among chromosome regions. The second chromosomes caused variation in both the amount and distribution of crossing over in a constant pair of *X* chromosomes; they caused the amount, but not the distribution, of crossing over to vary in a constant pair of third chromosomes. Thus, homologous and nonhomologous chromosomes can influence the amount and distribution of crossovers. These effects were observed when only the second chromosome varied; the real situation must be more complex when all the chromosomes vary.

The total amount of crossing over in the chromosomes varied by 12–14%. The most variable regions were the centromere and distal regions, which are generally most sensitive to influences on recombination. In one small region, crossing over varied twofold; in other regions, crossing over varied by 16–38%. Clearly, there is plenty of variation for recombination. That both the amount and distribution of crossing over can vary means that different regions can respond independently to selection pressures on recombination.

The effects of linked and unlinked modifiers can be compared. We looked at how linked modifiers affected recombination by seeing how the second chromosomes varied, since the rest of the genome was constant. How did modifiers that were on the second chromosome affect recombination rates in the second chromosome? We looked at how unlinked modifiers affected recombination by noting how these second chromosomes affected recombination in constant pairs of *X* and third chromosomes. Comparing the *X* with the second chromosome, the unlinked and linked modifiers caused the same form of variation; both the amount and distribution of crossing over varied, by comparable magnitudes. Comparing the third with the second chromosome, the unlinked and linked modifiers caused different forms of variation. For both chromosomes the amount of crossing over varied, by similar magnitudes. However, the linked but not the unlinked modifiers caused variation in the distribution of crossing over. Thus, unlinked modifiers can affect recombination to the same or to a lesser extent than can linked modifiers.

Selection experiments on recombination have provided examples of recombination modifiers. In *D. melanogaster,* KIDWELL (1972a,b), CHINNICI (1971a,b) and CHARLESWORTH and CHARLESWORTH (1985a,b) selected on the recombination rate in a chromosome region. KIDWELL and CHINNICI used mixtures of laboratory stocks, so that the variation responsible for selection response was not a sample from a natural population. CHARLESWORTH and CHARLESWORTH used flies from the same natural population used in these experiments to provide parts of the selected chromosome and the other chromosomes. The selection experiments show that the variation for recombination could be mo-

bilized; enough of the variation was additive for the lines to respond to selection.

At the end of the selection experiments, the selected lines were tested for the chromosomal distribution and specificity of recombination modifiers. Their results fit in with the sort of variation found in this experiment. Homologous and nonhomologous chromosomes can affect crossing over in a chromosome. Variation exists for the response to selection on recombination to be fairly specific to chromosome regions. Coarse scale variation can also contribute to the response in a particular region, resulting in some concordant responses in the unselected remainder of the chromosome. Their results indicating that modifiers can affect more than one region of the genome agree with these results; their results showing that several regions of the genome can affect recombination in a particular region complement these results.

The experiments reported here provide some indication of how elements of the final selection response in the selection experiments are related to the initial variation. For example, the correlations among regions and among chromosomes are present initially, rather than being built up over many generations of selection. The region-specific variation found in these experiments shows that lines with generally high crossing over may have regions with low crossing over. Therefore, the consistent positive association among regions of a chromosome in selected lines does not reflect the initial form of the variation.

Thus, the organization of the variation in nature is different from that after lines have been subject to selection. In selection experiments, genes that contribute to high or to low recombination in a region are accumulated in separate lines. In contrast, these experiments provide a "snapshot" of the variation as it is organized in a natural population. They show the form and magnitude of variation as it occurs naturally, something that selection experiments or looking at laboratory stocks cannot do.

In natural populations, selection on recombination may occur in several regions of the genome, rather than in a single region as in the recombination selection experiments. Selection may act on certain regions to reduce recombination and on others to increase it. The form of the variation, as it is organized in nature, shows how the response to these multiple selection pressures may occur. The region-specific variation found in these experiments implies that the various regions can respond to selection acting within those regions.

Within a standard laboratory line of *D. melanogaster*, without inversions, there is no association between the amount of crossing over on one chromosome and the amount on others (KRAMER and LEWIS 1956). The classic interchromosomal effect gives rise to negative associations [reviews by LUCCHESI (1976) and SCHULTZ and REDFIELD (1951)]; the gametes of structural heterozygotes show little or no crossing over around the inversion and show enhanced crossing over far from it and on other chromosomes, resulting in negative correlations among chromosomes for recombination. In contrast to this interchromosomal effect, in this study the associations among chromosomes were positive. We did not observe crossing over simultaneously in the same flies for

nonhomologous chromosomes, so we do not have data on the distribution of crossovers among the chromosomes within a line. Presumably the KRAMER and LEWIS result of no associations among the chromosomes within a line would apply. The positive association among chromosomes across lines exists because the lines differed in amount of crossing over, and all the chromosomes contributed to this difference. Lines with more crossing over in the second chromosome had more crossing over in the *X* and third chromosomes. This association among the chromosomes implies that there is some coarse control for amount of crossing over.

The causes for the variation in recombination rates among the lines are unknown. Deletions or inversions too small to be detected cytologically could cause lower recombination rates; these are not likely to be the major source of variation, however. The positive associations among regions on the same and different chromosomes are the opposite of the standard interchromosomal effect of inversions. In addition, of the six wild-type lines, only two had less crossing over and four had more than did the Oregon-R line. Inversions cannot explain why these lines had more crossing over than that on Oregon-R.

Many studies have shown that variation in heterochromatin affects recombination (MIKLOS and NANKIVELL 1976; review in JOHN 1973). The interchromosomal effect of heterochromatin deletions is similar to that of inversions in *D. melanogaster*. Females heterozygous or homozygous for *X* centromeric heterochromatin deletions have less recombination in the rest of the *X* (YAMAMOTO and MIKLOS 1978); heterozygous females have more recombination in the third chromosome (YAMAMOTO 1979). Centromeric heterochromatin influences recombination in the same chromosome by acting as a spacer between the euchromatin and the centromere, which reduces recombination in nearby euchromatin (YAMAMOTO and MIKLOS 1978; SZAUTER 1984). Variation in the amount of heterochromatin affects how strongly the euchromatin is exposed to the inhibitory effect of the centromere. Heterochromatin has been found to be quite variable in humans (CRAIG-HOLMES, MOORE and SHAW 1973) and in Bohemian wild mice (FOREJT 1973). Since heterochromatin affects crossing over on both the same and different chromosomes, differences in the distribution of heterochromatin may explain variation in recombination rates.

In *Neurospora crassa* there are genes that affect recombination at specific sites on the same or different chromosomes (see the summary in CATCHESIDE 1977). Meiotic mutants can affect the amount or distribution of crossing over, or both (review by BAKER *et al.* 1976). SANDLER *et al.* (1968) studied meiotic mutants from a natural population of *D. melanogaster* that had major effects on the amount of crossing over and on interference, which affects the distribution of crossing over. Perhaps variant alleles of small effect may contribute to genetic variation for recombination.

Whatever the mechanism underlying the variation, understanding the nature of the variation is necessary for understanding the evolution of recombination. Modifiers of recombination can affect multiple regions of the genome, as shown by these experiments, and single regions can be affected by multiple modifiers of recombination, as shown by selection experiments. These many-

to-many relationships among modifiers and the regions they affect mean that the evolutionary dynamics of recombination modifiers are complex. The positive associations for recombination among chromosome regions and among chromosomes imply that there are coarse controls of recombination. The coarse scale modifiers that contribute to selection response in one chromosome region will influence recombination in other regions as well. The variation specific to chromosome regions allows separate regions to respond independently to selection.

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