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Pairing for Recombination in LGV of *Caenorhabditis elegans*: A Model Based on Recombination in Deficiency Heterozygotes

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ABSTRACT

The effect of deficiencies on recombination was studied in *Caenorhabditis elegans*. Heterozygous deficiencies in the left half of linkage group V [LGV(left)] were shown to inhibit recombination to their right. Fourteen deficiencies, all to the left of *unc-46*, were analyzed for their effect on recombination along LGV. The deficiencies fell into two groups: 10 "major inhibitors" which reduce recombination to less than 11% of the expected rate between themselves and *unc-46*; and four "minor inhibitors" which reduce recombination, but to a much lesser extent. All four minor inhibitors delete the left-most known gene on the chromosome, while six of the ten major inhibitors do not (*i.e.*, these are "internal" deficiencies). Where recombination could be measured on both sides of a deficiency, recombination was inhibited to the right but not to the left. In order to explain these results we have erected a model for the manner in which pairing for recombination takes place. In doing so, we identify a new region of LGV, near the left terminus, that is important for the pairing process.

INTIMATE pairing between two homologs during the first meiotic division, described cytologically as "synapsis," is a progressive process which may initiate at one or multiple sites, depending on the particular bivalent studied. Crossing over, detected genetically, is correlated with synapsis (see MOSES, DRESSER and POORMAN 1984; VON WETTSTEIN, RASMUSSEN and HOLM 1984; JONES 1984; GIROUX 1988, for reviews). As yet, little is known about the mechanisms that determine where synapsis initiates and how it progresses along the chromosomes. This is especially true in the nematode *Caenorhabditis elegans*, where cytological studies of meiotic chromosomes have been quite limited. Detailed light microscopy of the pairing process is not possible, and only one set of investigators has studied this event in *C. elegans* using electron microscopy (GOLDSTEIN and SALTON 1981; GOLDSTEIN 1985). By means of serial section reconstruction, these workers demonstrated the presence of typical synaptonemal complexes in pachytene nuclei. Analyses of pairing in *C. elegans* have, therefore, relied principally on crossover and/or segregation data obtained with purely genetic techniques (reviewed by HERMAN 1988; ROSE and MCKIM 1989).

Most of the *C. elegans* information is derived from the behavior of chromosomes in either duplication or translocation heterozygotes. A third type of chromosomal rearrangement, the deficiency, has never been used to study meiosis in *C. elegans* and rarely in other organisms. Refering to deficiencies in general, LEFEVRE and MOORE (1967) wrote: "remarkably little attention has been paid to their effects on synapsis and crossing over." The present report documents the effects of heterozygous *C. elegans* deficiencies on recombination (crossing over) and analyzes these in relation to the pairing process.

Results from the previous duplication and translocation experiments have implicated a region, in each of five *C. elegans* chromosomes, that carries a homolog recognition site(s) necessary for recombination and disjunction along the chromosome [discussed by MCKIM, HOWELL and ROSE (1988), ROSE and MCKIM (1989) and by HERMAN and KARI (1989) for linkage group *X*]. An example is provided by the translocation *eT1(III;V)* (ROSENBLUTH and BAILLIE 1981) in which a reciprocal exchange had occurred between LGIII and LGV near the center of each chromosome. The two translocation chromosomes are *eT1(III)*, consisting of LGIII(left)LGV(left), and *eT1(V)*, consisting of LGV(right)LGIII(right). In *eT1* heterozygotes (*i.e.*, *normal LGIII/eT1;normal LGV/eT1*), recombination and disjunction occurs only between the LGIII(left) halves and between the LGV(right) halves. Thus, for LGIII and LGV, *cis*-acting homolog recognition sites regulating segregation and recombination appear to be localized in LGIII(left) and LGV(right) respectively.

In the course of establishing a detailed map of LGV(left) (ROSENBLUTH *et al.* 1988; JOHNSEN and BAILLIE 1988) we identified some LGV(left) deficiencies that, when heterozygous, inhibited recombination in adjacent regions to their right as far away as 17 map units (m.u.). This effect was not necessarily ex-

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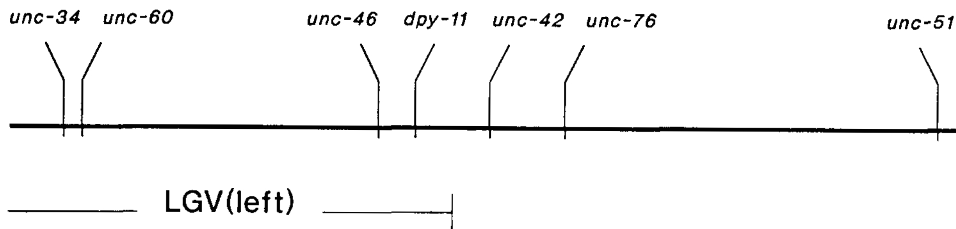


FIGURE 1.—Relationship of LGV-(left) to the whole LGV chromosome.

pected if recombination is regulated only in LGV(right) and if the only additional structural requirement for proper recombination is nucleotide homology. We therefore decided to compare the effects of a number of deficiencies whose breakpoints are distributed along LGV(left). Our results lead us to propose that pairing for recombination normally initiates in both halves of LGV at sites that act secondarily to the homolog recognition sites in LGV(right).

MATERIALS AND METHODS

C. elegans nematodes were cultured on Petri plates containing nematode growth medium streaked with *Escherichia coli* OP50 (BRENNER 1974). Unless otherwise indicated, all strains were derived from the wild type *C. elegans* strain N2 (var. Bristol). The nomenclature follows the uniform system adopted for *C. elegans* (HORVITZ *et al.* 1979).

Mutations: The "*s*" mutations were isolated in this laboratory. All other mutations were obtained from either the Medical Research Council stock collection in Cambridge, England, or from the Caenorhabditis Genetics Center at the University of Missouri, Columbia, MO. (1) *Nonlethal mutations*: LGIII: *dpy-18(e364)*. LGV: *unc-34(e566)*, *unc-60(e 677* and *m35)*, *unc-46(e177)*, *dpy-11(e224)*, *unc-42(e270)* and *unc-76(e911)*. The translocation *nT1(IV;V)* was isolated by FERGUSON and HORVITZ (1985) who found that it acted as a recombinational balancer for the right half of LGIV and the left half of LGV. Subsequently it has been found to balance also the *dpy-11–unc-76* region on LGV (CLARK *et al.* 1988). The reciprocal translocation *eT1(III;V)*) is a recombinational balancer for LGIII(right) and LGV(left) and was described by ROSENBLUTH and BAILLIE (1981). The mutations *dpy-11(s287)* and *unc-60(s1331)* are on eT1(III) (ROSENBLUTH and BAILLIE 1981; MCKIM, HOWELL and ROSE 1988). (2) *Mutations in essential genes on LGV*: The origins of the following recessive lethal mutations were described previously (ROSENBLUTH *et al. 1988*): *let-344(s376)*, *let-347(s1035)*, *let-419(s219)* and the lethal mutation *unc-62(s472)*. The mutation *let-326(s1404)* was recovered after 0.012 M ethylmethane sulfonate (EMS) mutagenesis (R. C. JOHNSEN, unpublished results). All the above lethal mutations were induced in the *eT1*-balanced region on *unc-46(e177)* marked chromosomes and were selected from "eT1" screens as described by ROSENBLUTH *et al.* (1988). The mutation *let-448(s1363)* was selected in a screen for *mut-4* induced lethals in the *nT1(IV;V)* balanced regions by CLARK *et al.* (1990). *mut-4* is a mutator derived from another *C. elegans* wild-type strain, BO (var. Bergerac), and is associated with the mobility of Tc1 transposable elements (MORI, MOERMAN and WATERSTON 1988). The lethal mutation *ama-2(m323)* was isolated and mapped to LGV by ROGALSKI, BULLERJAHN and RIDDLE (1988). (3) *LGV deficiencies*: All deficiencies had been previously isolated as recessive lethal mutations on *unc-46* marked chromosomes in "eT1" screens and had subsequently been identified as deficiencies. The origins of the following were described by ROSENBLUTH *et al.* (1988): *sDf27*, *sDf28*, *sDf33*, *sDf34* and *sDf38*, recovered after 1500 R γ-ray mutagenesis; *sDf39*, recovered after 500 R; *sDf32* and *sDf53*, recovered after 0.004 M and 0.012 M EMS mutagenesis, respectively. In the previous study the deficiencies *sDf38*, *sDf39* and *sDf53* had been classified simply as the alleles *s741*, *s521* and *s957* of the gene *let-336*. Subsequently it was found that all three failed to complement mutations in additional genes and were, therefore, reclassified as deficiencies (R. C. JOHNSEN, unpublished results). The origins of *sDf42* and *sDf50* were described by JOHNSEN and BAILLIE (1988). Both were recovered after 0.01% formaldehyde mutagenesis. The deficiency *sDf74* was recovered after treatment with ultraviolet-radiation (120J/M^2, using a germicidal lamp) by H. I. STEWART in this laboratory (personal communication). All the above deficiencies were selected from "eT1" screens. The deficiencies *sDf40*, *sDf45* and *sDf52* were selected as LGV *mut-4* induced lethals from the same screen as *let-448(s1363)* above (CLARK *et al.*, 1990).

Map positions: Figure 1 shows the relation of LGV(left) relative to the whole LGV chromosome. The positions of genes and deficiencies shown in Figure 2, were established prior to the present study. Much of the data has been published (EDGLEY and RIDDLE 1987; JOHNSEN and BAILLIE 1988). Data not previously published were obtained by R. C. JOHNSEN (unpublished results). These include the positions of the essential genes *let-448*, *let-437*, *let-453*, as well as the breakpoints of *sDfs 32, 34, 38, 39, 40, 45, 52 and 53*, The position of *sDf74* was mapped by H. I. STEWART (personal communication).

Recombination measurements: Since recombination rates have been shown to be temperature dependent (ROSE and BAILLIE 1979), all F_1 heterozygotes were raised at 20°.

Recombination measurements for Tables 1 and 2: Appropriate P_0 hermaphrodites were crossed with wild-type, N2, males; individual phenotypically wild-type F_1 hermaphrodites were picked and the F_2 progeny of the F_1s with the desired genotype were scored.

Recombination measurements for Table 4 (APPENDIX): To avoid picking a large number of F_1s that did not have the desired genotype, deficiency bearing male strains were constructed with the genotypes

+/*unc-60(s1331)eT1(III)sDf unc-46/eT1(V)*,

or +/*dpy-11(s287)eT1(III)sDf unc-46/eT1(V)*

or +/*eT1(III);sDf unc-46/unc-42eT1(V)*.

These were crossed to appropriate P_0 hermaphrodites; wild-type F_1 hermaphrodites were picked and the F_2 progeny from the correct F_1s were scored. For example, to measure recombination in the *ama-2–unc-76* interval (Table 4), +/*nT1(IV)*;+ *dpy-11 ama-2 unc-76/nT1(V)* hermaphrodites were crossed to +/*nT1(IV)*;*unc-46 dpy-11* + *unc-76/nT1(V)* males. The resulting Dpy Unc-76 hermaphrodites constituted the P_0s. These +/+;+ *dpy-11 ama-2 unc-76/unc-46 dpy-11* + *unc-76* hermaphrodites were crossed to +/*dpy-11(s287)eT1(III)*;*sDf unc-46* +++/*eT1(V)* males. Almost all the wild-type F_1s had the desired ++ *dpy-11 ama-2 unc-76/sDf unc-46* +++ genotype. In control experiments, a *let unc-*

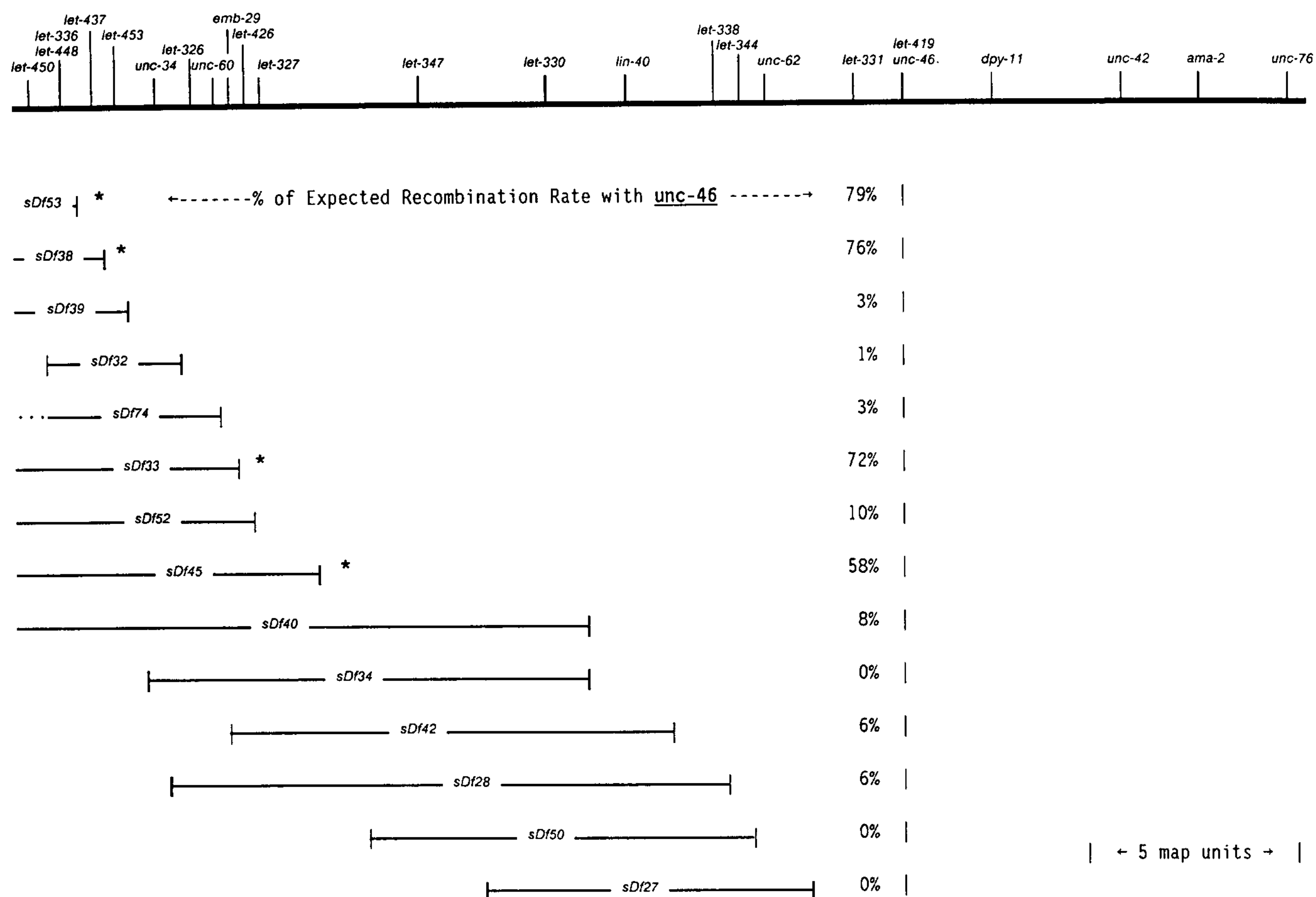


FIGURE 2.—Percent of expected recombination rate between *sDf* and *unc-46*. Measured in *dpy-18*/+;*sDf unc-46*/++ hermaphrodities. Minor inhibitors are marked with an asterisk, *. The position of the deficiencies were mapped previously (see MATERIALS AND METHODS). The map distances between *let-448* and *unc-60* are exaggerated for clarity. The map distance between *let-450* and *let-448* is not known.

46 chromosome was substituted for the *sDf unc-46* chromosome except in the case of the *unc-34 unc-60* interval, where the control chromosome was ++. The *let* was either *let-419* or *let-344*.

RESULTS

LGV(left) deficiencies fell into two groups: "major" and "minor" inhibitors of recombination: The breakpoints of the 14 LGV(left) deficiencies (*sDfs*), shown in Figure 2, had been localized by complementation mapping prior to this study (see MATERIALS AND METHODS). As can be seen, all deficiencies were to the left of *unc-46*(*V*) and each deletes at least five genes. *sDf53* deletes two more genes than shown; both lie in the *let-336* region (R. C. JOHNSEN, unpublished results).

The deficiencies had been isolated as lethal mutations on *unc-46*(*e177*)*V* marked chromosomes and were maintained balanced over *eT1*(*III;V*). In the first experiments we obtained recombination rates (in the absence of a balancer) between *unc-46* and the right-hand breakpoint of each deficiency, and compared these rates with those predicted. Table 1, column 4, gives the actual recombination rates in map units and column 6 expresses these in percent of the predicted rates. The latter were based on positions of markers near the respective breakpoints (see Table 2). Figure 2 summarizes the results (expressed as % of the expected rate). As can be seen, ten out of the 14 deficiencies severely inhibited recombination. Each recombined with *unc-46* at less than 11% of the expected frequency despite of the fact that some deficiencies were located at least 17 m.u. from *unc-46*. These ten deficiencies will be referred to as "major inhibitors," in contrast to the four "minor inhibitors," *sDf53, sDf38, sDf33* and *sDf45* (marked with an "*" on Table 1 and Figure 2). From the data in Table 1 it appeared that the deficiencies *sDf34*, *sDf50* and *sDf27* did not recombine at all with *unc-46*. This was somewhat misleading. In the course of subsequent experiments (below), recombination between the *sDfs* and *unc-46* was measured in a variety of genotypes (data not shown). The data from those experiments showed that *sDfs 34, 50* and *27* did recombine with *unc-46*, but at very low frequencies relative to the predicted ones.

Effects of deficiencies in specific intervals: To determine how far inhibition extended along LGV, effects of heterozygous deficiencies were measured across different intervals. The results are summarized in Table 3 and illustrated for the ten major inhibitors

TABLE 1

Recombination between *unc-46* and deficiencies, in *dpy-18/+;sDfx unc-46/++* hermaphrodites

Deficiency[a]	Unc-46 recombinants	F_2 adults	Recombination in map units: Actual[b]	Expected	Percent of expected
*sDf53**	134	2149	13.4 (11.0–15.9)	>17	<79
*sDf38**	132	2172	13.0 (10.7–15.6)	>17	<76
sDf39	3	2316	0.5 (0.1–0.7)	>17	<3
sDf32	1	2300	0.1 (0.0–0.5)	~16	~1
sDf74	2	1133	0.4 (0.1–1.2)	~16	~3[c]
*sDf33**	120	2344	10.8 (8.9–13.0)	~15	~72
sDf52	10	1305	1.5 (0.8–2.7)	~15	~10
*sDf45**	95	3067	6.4 (5.1–8.0)	>11	<58
sDf40	3	1294	0.5 (0.1–1.3)	>6	<8
sDf34	0	2263	0.0 (0.0–0.3)	>8	0
sDf42	2	2174	0.2 (0.0–0.6)	>3	<6
sDf28	1	3074	0.2 (0.0–0.3)	~3	~6
sDf50	0	1660	0.0 (0.0–0.4)	>2.5	0
sDf27	0	2619	0.0 (0.0–0.3)	>1.2	0

Data taken in part from Rosenbluth *et al.* (1988), Table 2; and Clark *et al.* (1990) results.

[a] * = "Minor" inhibitors (see text).

[b] One map unit = $100p$, where $p = 1 - [1 - 4(U46)]^{1/2}$, and where U46 is the frequency of Unc-46 recombinants. 95% confidence limits, in brackets, are based on limits of the recombinants which are taken from Table 1 of Crow and Gardner (1959).

[c] Data from H. I. Stewart (personal communication).

TABLE 2

Two-factor recombination data for genes on LGV(left)

Recombination interval	P_0 hermaphrodite[a]	F_1 progeny: Recombinants[b]	Total	Equation for p[c]	Distance in map units[d]
let-448 to *unc46*	*dpy-18/+;let-448 unc-46/++*	105 U46	1415	1	16.1 (12.8–19.8)
unc-34 to *unc-60*	*unc-34 unc-60(m35)/++*	22 U34	3896	1	1.1 (0.7–1.7)
let-326 to *unc-46*	*dpy-18/+;let-326(s238) unc-46/++*	126 U46	1592	1	17.3 (14.1–21.0)[e]
let-326 to *unc-46*	*dpy-18/+;let-326(s1404) unc/46/++*	265 U46	3660	1	15.7 (13.7–17.9)
unc-60 to *emb-29*	*unc-60(e677) emb-29 dpy-11/+++*	7 U60	2488	2	0.4 (0.2–0.8)[f]
unc-60 to *let-347*	*unc-60(m35) let-347 dpy-11/+++*	111 U60	4192	2	4.1 (3.3–4.8)
unc-60 to *dpy-11*	*unc-60(m35) dpy-11/++*	647 U60&D11	3979	3	17.8 (16.7–19.0)
let-327 to *unc-46*	*dpy-18/+;let-327 unc-46/++*	184 U46	2683	1	14.8 (12.5–17.3)[e]
let-347 to *dpy-11*	*unc-60(m35) let-347 dpy-11/+++*	339 D11	4192	2	13.0 (11.7–14.3)
let-330 to *unc-46*	*dpy-18/+;let-330 unc-46/++*	37 U46	943	1	8.3 (5.7–11.3)[e]
lin-40 to *dpy-11*	*lin-40(e2173) dpy-11/++*	97 D11	2391[g]	1	8.5 (6.8–10.3)[e]
let-338 to *unc-46*	*dpy-18/+;let-338 unc-46/++*	74 U46	4351	1	3.5 (2.7–4.3)[e]
let-344 to *unc-46*	*dpy-18/+;let-344 unc-46/++*	18 U46	1276	1	2.9 (1.8–4.4)[e]
unc-62 to *unc-46*	*dpy-18/+; unc-62 unc-46/++*	26 U46	1925	1	2.7 (1.8–4.0)[e]
unc-62 to *dpy-11*	*unc-62 dpy-11/++*	102 D11	3046	2	5.2 (4.2–6.2)
let-331 to *unc-46*	*+ let-331 unc-46 +/unc-60 ++ dpy-11*	7 U46	894	2	1.2 (0.6–2.3)[e]
unc-46 to *dpy-11*	*unc-46 dpy-11/++*	71 U46&D11	3337	3	2.1 (1.7–2.7)

[a] See materials and methods for alleles used in new data.

[b] Abbreviations for phenotypes: U46 = Unc-46; U34 = Unc-34; U60 = Unc-60; D11 = Dpy-11.

[c] Equations for the recombination frequency, p, where R = frequency of recombinants scored:

$$p = 1 - (1 - 4R)^{1/2} \quad (1)$$

$$p = 1 - (1 - 3R)^{1/2} \quad (2)$$

$$p = 1 - (1 - 2R)^{1/2} \quad (3)$$

[d] One map unit = $100p$. The 95% confidence limits (in parentheses) are based on the limits of the recombinants. These limits are either taken from Table 1 of Crow and Gardner (1959), or, $= 2[Nq(1 - q)]^{1/2}$ where N = total F_1s and q = frequency of recombinants (for >300 recombinants).

[e] Data taken from Rosenbluth *et al.* (1988).

[f] Data taken from McKim, Howell and Rose (1988).

[g] Includes larval F_1s.

TABLE 3

Summarized effects of deficiency heterozygotes on crossing over in LGV intervals

Deficiency[a]	Percent recombination of control value in different intervals[b]						
	unc-34–unc-60	*unc-60–let-347*	*unc-62–dpy-11*	*unc-46–dpy-11*	*dpy-11–unc-42*	*unc-42–ama-2*	*ama-2–unc-76*
Control	100.0 (63.6–154.5)	100.0 (81.4–123.3)	100.0 (84.2–116.1)	100.0 (71.2–137.2)	100.0 (82.1–117.8)	100.0 (75.1–124.9)	100.0 (72.0–134.7)
*sDf53**	ND	72.1 (55.8–93.0)	86.8 (67.9–103.8)	ND	ND	ND	ND
*sDf38**	ND	62.8 (46.5–76.7)	75.5 (60.4–92.5)	ND	ND	ND	ND
sDf39	ND	2.3 (0.0–11.6)	7.5 (3.8–13.2)	ND	23.2 (13.7–32.7)	75.2 (50.3–100.0)	128.6 (95.2–176.2)
sDf32	#	0.0 (0.0–4.7)	5.7 (3.8–11.3)	ND	0.0 (0.0–2.0)	126.6 (84.2–175.7)	128.6 (85.7–181.0)
sDf74	#	#	15.1 (7.5–22.6)	ND	52.6 (40.4–66.6)	ND	133.3 (95.2–176.2)
*sDf33**	#	#	71.7 (48.8–95.7)	ND	ND	ND	ND
sDf52	#	#	15.1 (7.5–22.6)	ND	34.4 (23.8–47.4)	ND	50.5 (30.5–80.9)
*sDf45**	#	#	34.0 (20.8–49.1)	ND	ND	ND	ND
sDf40	#	#	3.8 (1.9–11.3)	ND	16.2 (10.3–23.5)	ND	100.0 (61.9–142.9)
sDf34	#	#	3.8 (1.9–11.3)	ND	8.3 (4.6–20.8)	57.1 (37.3–77.4)	81.0 (57.1–104.8)
sDf42	118.2 (72.7–172.7)	#	13.2 (5.7–20.8)	ND	25.2 (17.2–35.1)	113.0 (83.1–149.7)	66.7 (47.6–85.7)
sDf28	#	#	3.8 (1.9–9.4)	ND	13.9 (7.6–23.5)	65.5 (42.4–97.2)	104.8 (71.4–147.6)
sDf50	ND	#	5.7 (1.9–11.3)	ND	18.0 (10.7–25.7)	100.6 (70.1–131.2)	ND
sDf27	ND	104.7 (86.0–132.6)	#	21.9 (9.8–47.0)	43.0 (33.1–53.0)	ND	95.2 (71.4–119.0)

[a] * = "Minor" inhibitor.
[b] The 95% confidence limits are in brackets. ND = not determined; # = deficiency extends into the interval.

in Figure 3. (The actual data are given in Table 4 in the APPENDIX.) For most deficiencies, recombination could be measured only in intervals to the right of the deficiency. However, in two cases it could also be measured to the left (*i.e.*, from *unc-34* to *unc-60* for *sDf42*; from *unc-60* to *let-347* for *sDf27*).

Two features of the results were significant. The first was the similarity with which recombination in specific intervals to the right was affected by the major inhibitors, in spite of the fact that their right-hand breakpoints varied considerably: Some were as much as 18 m.u. from *dpy-11* (*sDfs 39* and *32*) while others were only 5–6 m.u. away (*sDfs 28, 50* and *27*). Inhibition by all ten deficiencies reduced recombination to less than 16% of control in the *unc-62–dpy-11* interval and in most cases had disappeared by the *ama-2–unc-76* interval.

The second significant feature of the results became evident through the comparison of measurements in the left-hand intervals with those in the right-hand ones. The data for *sDf42* and *sDf27* indicated that, while both deficiencies inhibited recombination to their right, there was no corresponding inhibition to their left. This uneven inhibition could also be demonstrated with *sDf50*, by comparing recombination between the *unc-60–sDf50* and the *unc-62–dpy-11* intervals. Hermaphrodites with the genotype *unc-60(m35) + unc-62 + dpy-11/+ sDf50 + unc-46 +* produced 61 Unc-60s and 8 Dpy-11s among a total of 2336 adult progeny. The Dpy-11s were due to recombination between *unc-62* and *dpy-11*, giving an apparent map distance of 0.3 m.u. for this interval instead of the normal 5.3. Thus here, on the right, *sDf50* heterozygosity decreased recombination to 6% of the normal rate. The Unc-60s were due to recombination between *unc-60* and *unc-62*, occurring both to the left and to the right of *sDf50* (Figure 3). They represented an apparent recombination distance of 2.6 m.u. As is evident from the figure, only a negligible part of this recombination could have been to the right of *sDf50; i.e.*, 6% of 0.5 m.u. (the approximate distance between *let-344* and *unc-62*; Table 2). Therefore, the 2.6 m.u. represented recombination between *unc-60* and the left-hand breakpoint of *sDf50*. Since the actual distance could be no more than 4.1 m.u. (the normal *unc-60* to *let-347* distance, Table 2), recombination to the immediate left of *sDf50* was at least 63% of the normal rate, which was in sharp contrast to only 6% on the right.

DISCUSSION

Our study has shown that a series of heterozygous LGV(left) deficiencies are associated with inhibition of recombination in adjacent regions to their right. The severity and extent of inhibition associated with

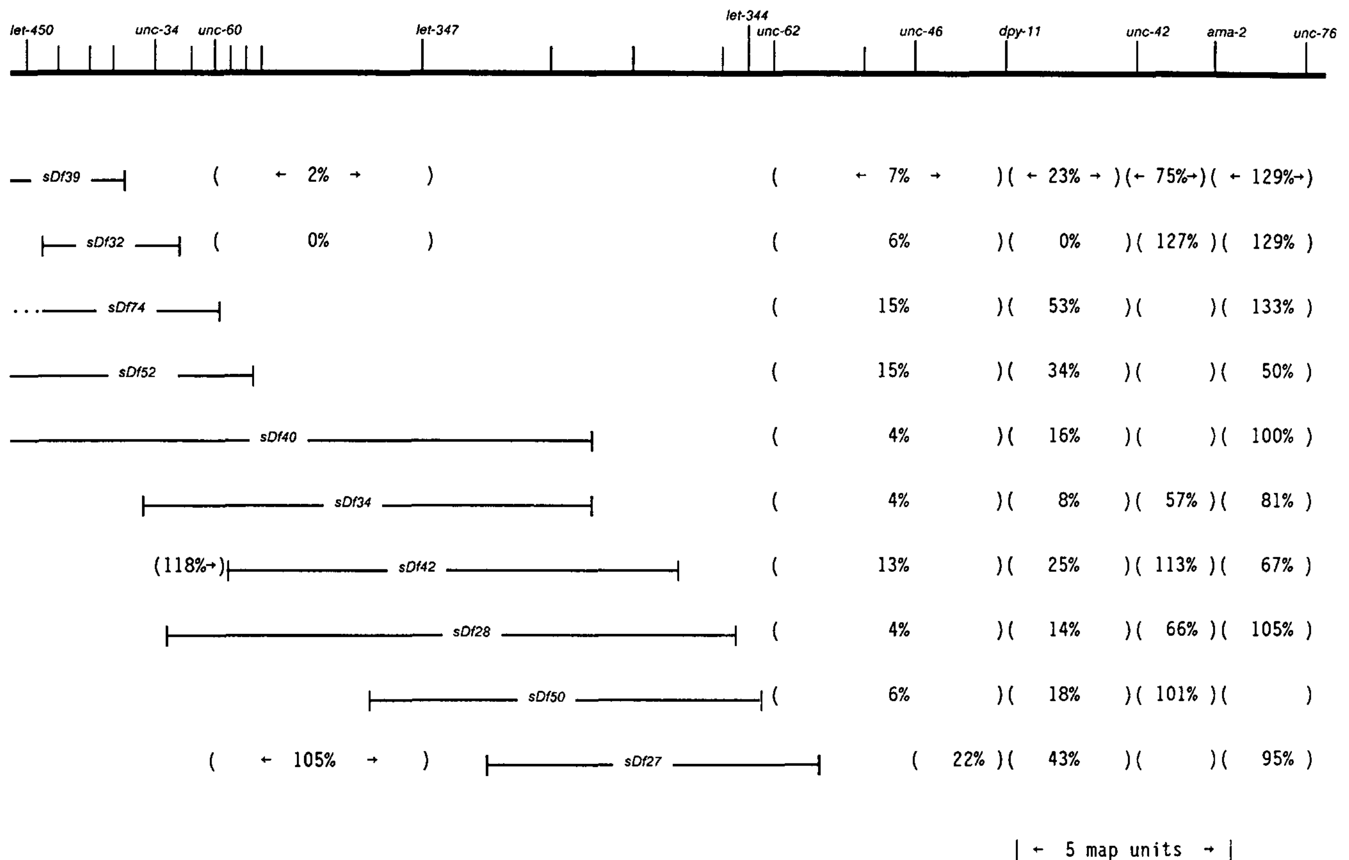
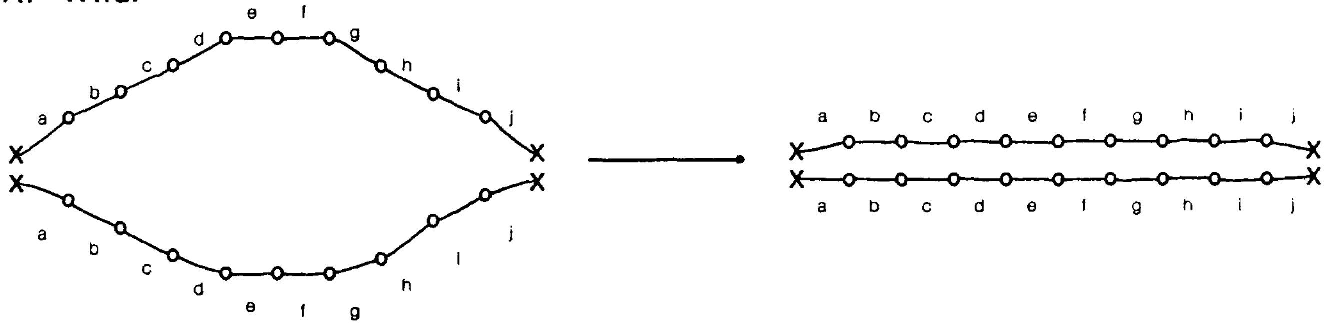


FIGURE 3.—Percent of control recombination in different LGV intervals, in *sDf* heterozygotes. The effects of only the major inhibitors are shown.

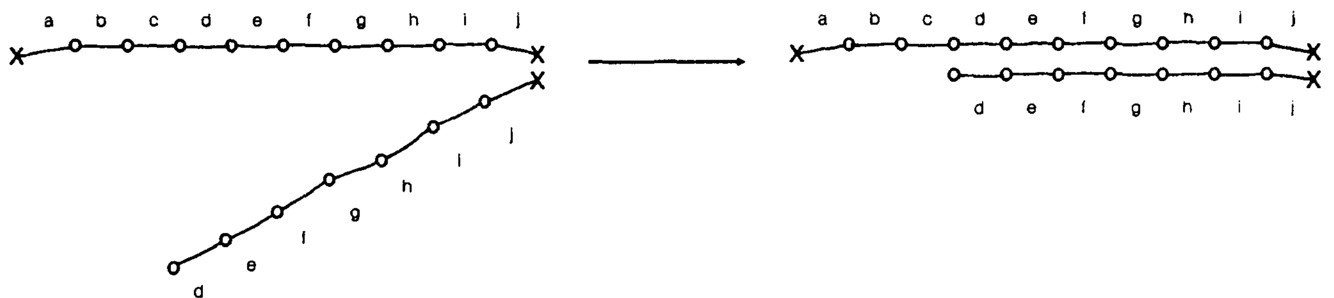
some deficiencies is surprising. With *sDf39, sDf32* and *sDf74* recombination is inhibited by more than 95% over a region of at least 16 map units. Deficiencies are generally not considered to be significant crossover suppressors. ROBERTS (1970) screened for, and selected, more than 100 dominant crossover suppressors in *Drosophila melanogaster*. He examined their salivary gland chromosomes for chromosomal rearrangements. In almost all of them he detected either an inversion, a transposition or a translocation, but made no mention of detecting any deficiencies. We have found only a few cases in the literature where the effects of deficiencies on recombination were reported (BRIDGES, SKOOG and LI 1936; STADLER and ROMAN 1948; LEFEVRE and MOORE 1967; CHOVNICK, BALLANTYNE and HOLM 1971; YAMAMOTO and MIKLOS 1978; CLARK *et al.* 1986; HILLIKER, CLARK and CHOVNICK 1988). These reports cited either a smaller degree of inhibition or none at all.

The possibility exists, of course, that our severe inhibitory effects are not due to the deficiencies themselves but rather due to associated other rearrangements such as inversions or translocations. However, while we cannot rule out this possibility, we think it is highly unlikely that 10 out of 14 LGV(left) deficiencies are associated with rearrangements affecting the adjacent right-hand regions. Except for terminal deficiencies recovered as half-translocations, such rearrangements would require more than two breaks. Six of the ten major inhibitors are clearly not terminal deficiencies (Figure 2). We believe the chance of these being associated with additional breakpoints is very low, based on the mutagen treatments they were recovered from: 1500 R γ-irradiation, 0.01% formaldehyde or 0.004 M EMS. For γ-irradiation, ROSENBLUTH, CUDDEFORD and BAILLIE (1985) estimated that about 5% of 1500 R treated gametes carrying a chromosomal rearrangement would carry a second one. For formaldehyde, based on a comparison of brood sizes from heterozygotes bearing lethals induced by 0.012 M EMS, 1500 R, or 0.07–0.18% formaldehyde (JOHNSEN and BAILLIE 1988), we believe our formaldehyde-induced deficiencies are less likely to be associated with additional rearrangements than the gamma ray induced ones. Furthermore, calculation of progeny broods per hermaphrodite from data in Table 4 rule out the possibility that any major inhibitors were associated with translocations of the type that do not permit aneuploid progeny to survive. From hermaphrodites, heterozygous for this type of translocation, only 36% of the zygotes survive (HERMAN 1978; ROSENBLUTH and BAILLIE 1981). For each major inhibitor the average progeny brood size from heterozygous hermaphrodites was at least 75% (and in most cases at least 85%) of the average control brood.

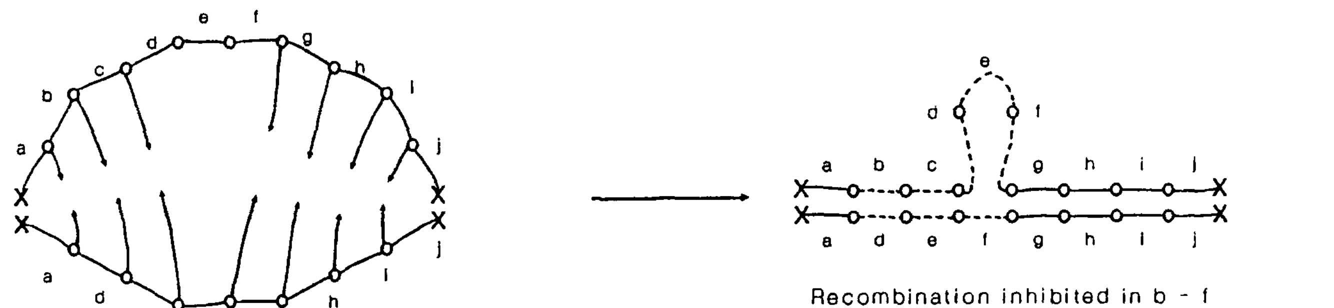
A. Wild:



B. Heterozygote for a - c deficiency:



C. Heterozygote for b - c deficiency:



X = Site at which pairing for recombination initiates.

o = Alignment site.

---- = Regions in which recombination is inhibited.

FIGURE 4.—Proposed pairing for recombination along LGV. a, b, c, ... j are chromosomal regions.

Characteristics of the inhibition associated with LGV(left) deficiencies: There are three salient aspects of the inhibition: (1) Based on the severity of inhibition, the deficiencies fall into two classes, namely ten major inhibitors and four minor inhibitors. Figure 2 shows no obvious differences between these two classes of deficiencies. Deletion of specific sites by major but not by minor inhibitors cannot account for the difference between the severe effects on recombination produced by *sDf32* and the minor effects by *sDf33* and *sDf45*. The latter two deficiencies deleted the same region as *sDf32*, in addition to regions on either side. For this reason, a size difference also cannot account for the different effects. (2) Where it was possible to measure recombination on both sides of a deficiency, recombination was inhibited on one adjacent side but not the other. The deficiencies *sDf 42, 50* and *27*, as heterozygotes, inhibit recombination to the right but do not have a corresponding effect on the left. (3) The right-hand breakpoints do not determine how far LGV(left) deficiencies inhibit recombination to their right. Inhibition by nine defi-

ciencies extends to, and ends within, the same 5 m.u. interval (between *dpy-11* and *ama-2*), despite the fact that some of the breakpoints are as much as 12 m.u. apart.

How can the inhibition be explained? The simplest explanation would only require the existence of specific sites, necessary for recombination, that are deleted by the major inhibitors. There would have to be several such sites: at least one that is deleted by *sDf32* and is to the left of *unc-34*, to account for inhibition by *sDfs 39, 32, 52* and *74*; and another in the *let-330* region, to account for inhibition by the other deficiencies shown in Figure 3. However, while deletion of a specific site(s) may be necessary, it is not sufficient to explain inhibition by *sDf32* since (as has already been pointed out) such a site would also be deleted by *sDfs 33* and *45*, each of which cause only minor inhibition. To explain the inhibition we will present a model for the manner in which pairing for recombination takes place along LGV.

Minor inhibitors may delete a special site(s) near the left terminus that is not deleted by major ones: Before describing the model for pairing, we postulate the existence of a special site, deleted by minor but not major inhibitors, that is responsible for the difference between the two classes. The site's existence is based on the following. Among the 14 deficiencies studied, six do not delete the left-most marker, *let-450* (Figure 2), and therefore are "internal" deficiencies. These six are all major inhibitors. We hypothesize that the remaining four major inhibitors (*sDfs 39, 74, 52* and *40*) are also internal deficiencies and do not extend as far to the left as do the four minor inhibitors (*sDfs 53, 38, 33* and *45*) each of which deletes *let-450*. Since it is not known how far LGV extends to the left beyond *let-450*, the hypothesis is plausible and places the postulated site to the left of *let-450*.

A model for recombination pairing in LGV: The model proposes that pairing for recombination involves at least two types of chromosomal sites, which we will refer to as "initiation sites" and "alignment sites." Intimate pairing for recombination starts at and spreads from each initiation site, if homologous sites are within a minimum distance of each other. We consider the initiation sites to be analogous to the pairing sites mapped by HAWLEY (1980) in *D. melanogaster*. We propose that the special site we postulated above (at or near the left terminus) is such an initiation site for LGV(left) (Figure 4, A). Another site must exist in LGV(right) to account for recombination occurring in that region in *eT1(III;V)* translocation heterozygotes (see Introduction). For simplicity we have assumed only one initiation site for LGV(right), located near the right end. The pairing process spreads from each initiation site by "buttoning-up" the homologs at sequential alignment sites, which are ones that occur repeatedly between initiation sites and have a common sequence. In the presence of a heterozygous minor inhibitor, there are no homologous left-end initiation sites. Pairing initiates only in LGV(right) (Figure 4B), proceeds towards the left, aligns the homologs in a correct manner (*i.e.*, homologous regions remain in register) and no major inhibition of recombination occurs. On the other hand, in the presence of a heterozygous major inhibitor (which does not delete the initiation site), pairing proceeds from both ends of LGV (Figure 4C). To the left of the deficiency, homologous regions remain in register (*i.e.* region "*a*") and recombine normally. But to its right, the sequential buttoning of alignment sites causes a misalignment: heterologous regions become aligned, thus inhibiting recombination. This misalignment continues until a region is reached whose alignment is controlled by pairing that initiated at the right end. To explain the disappearance of inhibition in the *ama-2* region, we propose that the speed at which pairing occurs from each end is such that alignment of the *ama-2* region is mainly controlled from the right and therefore remains normal, while the alignment of the *unc-62* region (on the left) is still controlled by pairing that initiated at the left end and is not normal. Based on our current data, there would be a minimum of three alignment sites in LGV(left): One in the *sDf32* region, one in the *let-330* region and one between *sDf27* and *dpy-11*. Finding small deficiencies, within these three regions, that still inhibit recombination would localize the alignment sites more precisely. Alternatively, new LGV(left) deficiencies lying outside these regions would either identify more alignment sites or indicate that they lie between two such sites, depending on whether or not they inhibit recombination.

How does the pairing model relate to the findings from translocation and duplication experiments? Those findings implicate regions for each of five chromosomes as ones in which homolog recognition sites, necessary for the segregation and recombination of their respective chromosomes, are located (referenced in the Introduction). For LGV, a homolog recognition site is believed to be localized in LGV(right) based on translocation experiments (ROSENBLUTH and BAILLIE 1981; HERMAN, KARI and HARTMAN 1982; FERGUSON and HORVITZ 1985). The current model, proposing an initiation for pairing site in LGV(left), is not inconsistent with those findings. It simply extends them by defining a type of site that acts secondarily to the homolog recognition site. That is, a prerequisite for pairing to occur at an initiation site is that the pairing partners must carry identical homolog recognition sites. Thus, the initiation sites in an *eT1(III;V)* heterozygote are not sufficient to permit recombination between the two LGV(left) regions because these regions are associated with different homolog recognition sites: The LGV(left) on the translocation chro-

mosome is associated with the LGIII recognition site while LGV(left) on the normal chromosome is associated with the LGV one.

In the case of duplications, such as those for LGI (ROSE, BAILLIE and CURRAN 1984) and LGX (HERMAN and KARI 1989), duplications for only one end of each chromosome recombine with their normal homolog. The duplications for the opposite ends may still have initiation sites but lack sites for homolog recognition.

Deficiencies do not cause inhibition by moving regions closer to an inhibitor site at the left: Here we reject an alternative model to explain our inhibitory effects. This model is suggested by findings in *D. melanogaster*, where reduction of recombination in chromosomal segments, repositioned closer to the centromere, has been attributed to an inhibitory effect of the centromere (BEADLE 1932; MATHER 1939; YAMAMOTO and MIKLOS 1978). If the *C. elegans* site we postulate as being near the left terminus (and deleted by minor inhibitors) acted as a recombination inhibitor, the severe inhibition in regions to the right might be due to the regions being moved closer to this site. The fact that the heterozygous major and minor inhibitors had different effects would then be due to the latter's deletion of the *cis*-linked inhibitor. We consider this an unlikely model for the following reason. Deletion of the *cis*-linked inhibitor site by minor inhibitors should have caused increased recombination adjacent to these deficiencies. Instead we observed minor inhibition. To maintain the idea of an inhibitor site, one would have to postulate that any potential increase of recombination was counteracted by the haploid site on the normal chromosome.

Summary and conclusion: We have reported the effects of heterozygous deficiencies on recombination in *C. elegans*. We found that deficiencies in LGV(left) cause inhibition to their right and that this inhibition was severe for 10 out of the 14 deficiencies. Where recombination was studied on both sides of the deficiency, inhibition occurred only toward their right. To explain our data we propose a model for recombination pairing, and postulate the existence of special sites (initiation and alignment sites) that act secondarily to the homolog recognition site believed to be in LGV(right).

Finally, the study has shown deficiencies to be useful as probes for the analysis of meiotic pairing in *C. elegans*. It focuses attention on a new region of LGV (the left end) as potentially important for the pairing process.

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APPENDIX

Table 4 presents the data which were summarized in Table 3 and Figure 3 (RESULTS), *i.e.*, the effects of deficiencies on recombination in different intervals on LGV. The genotypes from which F_2s were scored are shown in column 2. Column 4 gives the F_2 progeny from which the recombination distances (column 6) were calculated. The phenotype of the recombinant class scored is indicated in each case, as are the total number of adult progeny. Column 7 shows the recombination distance in percentage of the control values.

TABLE 4

Effect of different deficiency heterozygotes on recombination in specific LGV intervals

Interval	F_1 genotype	Deficiency	F_2 recombinant/ total (N)[a]	Equation[b]	m.u. = 100p[c]	Percent of control
unc-34–unc-60			Unc-34/total			
	unc-34 unc-60[d]*/++*	Control[e]	22/3896 (12)	4	1.1 (0.7–1.7)	100.0 (63.6–154.5)
	unc-34 unc-60 ++/++ sDf unc-46	*sDf42*	21/2521 (10)	3	1.3 (0.8–1.9)	118.2 (72.7–172.7)
unc-60–let-347			Unc-60/total			
	unc-60 let-347 ++ dpy-11/++ let unc-46 +	Control[f]	88/2447 (16)	5	4.3 (3.5–5.3)	100.0 (81.4–123.3)
	+ unc-60 let-347 + dpy-11/sDf ++ unc-46 +	*sDf53*	60/1941 (11)	2	3.1 (2.4–4.0)	72.1 (55.8–93.0)
	+ unc-60 let-347 + dpy-11/sDf ++ unc-46 +	*sDf38*	68/2441 (14)		2.7 (2.0–3.3)	62.8 (46.5–76.7)
	+ unc-60 let-347 + dpy-11/sDf ++ unc-46 +	*sDf39*	1/1092 (7)		0.1 (0.0–0.5)	2.3 (0.0–11.6)
	+ unc-60 let-347 + dpy-11/sDf ++ unc-46 +	*sDf32*	0/2039 (13)		0.0 (0.0–0.2)	0.0 (0.0–4.7)
	unc-60 let-347 ++ dpy-11/++ sDf unc-46 +	*sDf27*	110/2476 (15)		4.5 (3.7–5.5)	104.7 (86.0–132.6)
unc-62[g]*–dpy-11*			Dpy/total			
	+ unc-62 + dpy-11/let + unc-46 +	Controls[f,h]	159/3067 (17)	2	5.3 (4.5–6.2)	100.0 (84.2–116.1)
	+ unc-62 + dpy-11/sDf + unc-46 +	*sDf53*	91/2074 (13)		4.6 (3.6–5.5)	86.8 (67.9–103.8)
	+ unc-62 + dpy-11/sDf + unc-46 +	*sDf38*	83/2111 (13)		4.0 (3.2–4.9)	75.5 (60.4–92.5)
	+ unc-62 + dpy-11/sDf + unc-46 +	*sDf39*	7/1972 (12)		0.4 (0.2–0.7)	7.5 (3.8–13.2)
	+ unc-62 + dpy-11/sDf + unc-46 +	*sDf32*	7/2222 (15)		0.3 (0.2–0.6)	5.7 (3.8–11.3)
	+ unc-62 + dpy-11/sDf + unc-46 +	*sDf74*	17/2181 (14)		0.8 (0.4–1.2)	15.1 (7.5–22.6)
	+ unc-62 + dpy-11/sDf + unc-46 +	*sDf33*	41/1109 (13)		3.8 (2.6–5.1)	71.7 (48.8–95.7)
	+ unc-62 + dpy-11/sDf + unc-46 +	*sDf52*	13/1733 (13)		0.8 (0.4–1.2)	15.1 (7.5–22.6)
	+ unc-62 + dpy-11/sDf + unc-46 +	*sDf45*	24/1353 (13)		1.8 (1.1–2.6)	34.0 (20.8–49.1)
	+ unc-62 + dpy-11/sDf + unc-46 +	*sDf40*	3/1475 (16)		0.2 (0.1–0.6)	3.8 (1.9–11.3)
	+ unc-62 + dpy-11/sDf + unc-46 +	*sDf34*	4/1747 (14)		0.2 (0.1–0.6)	3.8 (1.9–11.3)

TABLE 4—Continued

Interval	F_1 genotype	Deficiency	F_2 recombinant/ total $(N)^a$	Equation[b]	m.u. = $100p^c$	Percent of control
	+ unc-62 + dpy-11/sDf + unc-46 +	*sDf42*	13/1976 (12)		0.7 (0.3–1.1)	13.2 (5.7–20.8)
	+ unc-62 + dpy-11/sDf + unc-46 +	*sDf28*	3/1598 (12)		0.2 (0.1–0.5)	3.8 (1.9–9.4)
	unc-60 + unc-62 + dpy-11/+sDf + unc-46 +	*sDf50*	8/2336 (12)		0.3 (0.1–0.6)	5.7 (1.9–11.3)
unc-46–dpy-11			Dpy/total			
	+++/let unc-46 dpy-11	Control[f]	37/2604 (11)	3	2.2 (1.5–2.9)	100.0 (71.2–137.2)
	+++/sDf unc-46 dpy-11	*sDf27*	6/1904 (10)		0.5 (0.2–1.0)	21.9 (9.8–47.0)
dpy-11–unc-42			Dpy & Unc-42/total			
	++ dpy-11 unc-42/let unc-46 ++	Control[h]	111/2800 (11)	1	3.0 (2.5–3.6)	100.0 (82.1–117.8)
	++ dpy-11 unc-42/sDf unc-46 ++	*sDf39*	23/2474 (10)		0.7 (0.4–1.0)	23.2 (13.7–32.7)
	++ dpy-11 unc-42/sDf unc-46 ++	*sDf32*	0/3882 (17)		0.0 (0.0–0.1)	0.0 (0.0–2.0)
	++ dpy-11 unc-42/sDf unc-46 ++	*sDf74*	61/2909 (13)		1.6 (1.2–2.0)	52.6 (40.4–66.6)
	++ dpy-11 unc-42/sDf unc-46 ++	*sDf52*	33/2395 (13)		1.0 (0.7–1.4)	34.4 (23.8–47.4)
	++ dpy-11 unc-42/sDf unc-46 ++	*sDf40*	24/3663 (16)		0.5 (0.3–0.7)	16.2 (10.3–23.5)
	++ dpy-11 unc-42/sDf unc-46 ++	*sDf34*	8/2380 (10)		0.3 (0.1–0.6)	8.3 (4.6–20.8)
	++ dpy-11 unc-42/sDf unc-46 ++	*sDf42*	31/3086 (11)		0.7 (0.5–1.1)	25.2 (17.2–35.1)
	++ dpy-11 unc-42/sDf unc-46 ++	*sDf28*	12/2164 (9)		0.4 (0.2–0.7)	13.9 (7.6–23.5)
	++ dpy-11 unc-42/sDf unc-46 ++	*sDf50*	22/3086 (12)		0.5 (0.3–0.8)	18.0 (10.7–25.7)
	++ dpy-11 unc-42/sDf unc-46 ++	*sDf27*	84/4875 (17)		1.3 (1.0–1.6)	43.0 (33.1–53.0)
unc-42–ama-2[i]			Unc-42/total			
	++ unc-42 ama-2/let unc-46 ++	Controls[f,h]	59/3354 (22)	2	1.8 (1.3–2.2)	100.0 (75.1–124.9)
	++ unc-42 ama-2/sDf unc-46 ++	*sDf39*	34/2577 (19)		1.3 (0.9–1.8)	75.2 (50.3–100.0)
	++ unc-42 ama-2/sDf unc-46 ++	*sDf32*	32/1445 (11)		2.2 (1.5–3.1)	126.6 (84.2–175.7)
	++ unc-42 ama-2/sDf unc-46 ++	*sDf34*	28/2799 (20)		1.0 (0.7–1.4)	57.1 (37.3–77.4)
	++ unc-42 ama-2/sDf unc-46 ++	*sDf42*	43/2172 (13)		2.0 (1.5–2.7)	113.0 (83.1–149.7)
	++ unc-42 ama-2/sDf unc-46 ++	*sDf28*	23/1997 (12)		1.2 (0.8–1.7)	65.5 (42.4–97.2)
	++ unc-42 ama-2/sDf unc-46 ++	*sDf50*	40/2272 (12)		1.8 (1.2–2.3)	100.6 (70.1–131.2)
ama-2[i]*–unc-76*			Unc-76/total			
	++ dpy-11 ama-2 unc-76/let unc-46 +++	Control[f]	40/2093 (13)	6	2.1 (1.5–2.8)	100.0 (71.4–133.3)
	++ dpy-11 ama-2 unc-76/sDf unc-46 +++	*sDf39*	40/1490 (11)	2	2.7 (2.0–3.7)	128.6 (95.2–176.2)
	++ dpy-11 ama-2 unc-76/sDf unc-46 +++	*sDf32*	32/1197 (9)		2.7 (1.8–3.8)	128.6 (85.7–181.0)
	++ dpy-11 ama-2 unc-76/sDf unc-46 +++	*sDf74*	44/1604 (13)		2.8 (2.0–3.7)	133.3 (95.2–176.2)
	++ dpy-11 ama-2 unc-76/sDf unc-46 +++	*sDf52*	16/1514 (13)		1.1 (0.6–1.7)	50.5 (30.5–80.9)
	++ dpy-11 ama-2 unc-76/sDf unc-46 +++	*sDf40*	26/1272 (11)		2.1 (1.3–3.0)	100.0 (61.9–142.9)
	++ dpy-11 ama-2 unc-76/sDf unc-46 +++	*sDf34*	39/2377 (18)		1.7 (1.2–2.2)	81.0 (57.1–104.8)
	++ dpy-11 ama-2 unc-76/sDf unc-46 +++	*sDf42*	43/3142 (18)		1.4 (1.0–1.8)	66.7 (47.6–85.7)
	++ dpy-11 ama-2 unc-76/sDf unc-46 +++	*sDf28*	34/1561 (10)		2.2 (1.5–3.1)	104.8 (71.4–147.6)
	++ dpy-11 ama-2 unc-76/sDf unc-46 +++	*sDf27*	53/2733 (15)		2.0 (1.5–2.5)	95.2 (71.4–119.0)

[a] Recombinant F_2s scored/total adults. Number in parentheses = number of F_1 hermaphrodites.

[b] Equations for the recombination frequency, p, where R = frequency of recombinant class scored:

$$p = 1 - (1 - 1.5R)^{1/2} \quad (1)$$

$$p = 1 - (1 - 2R)^{1/2} \quad (2)$$

$$p = 1 - (1 - 3R)^{1/2} \quad (3)$$

$$p = 1 - (1 - 4R)^{1/2} \quad (4)$$

$$p = 0.445 - (0.1975 - R)^{1/2} \text{ (assuming } let\text{-}347\text{–}dpy\text{-}11 = 13 \text{ m.u. and } unc\text{-}46\text{–}dpy\text{-}11 = 2 \text{ m.u.)} \quad (5)$$

$$p = 0.465 - (0.216 - R)^{1/2} \text{ (assuming } unc\text{-}46\text{–}ama\text{-}2 = 7 \text{ m.u.)} \quad (6)$$

[c] The 95% confidence limits (in brackets) are based on the limits of the recombinants. These limits are taken from Table 1 of CROW and GARDNER (1959).

[d] *unc-60* allele used throughout this table is *m35*.

[e] Control chromosome is ++.

[f] Control chromosome is *let-419 unc-46*.

[g] The allele *unc-62(s472)* is a recessive lethal.

[h] Control chromosome is *let-344 unc-46*.

[i] The allele *ama-2(m323)* is a recessive lethal.